Report of the NCI-CDC Working Group to Revise

the 1985 NIH Radioepidemiological Tables

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I. Executive Summary

The legislative mandate for the 1985 Report of the NIH Ad Hoc Working Group to Develop Radioepidemiological Tables provided for analyses of existing data linking cancer risk to ionizing radiation exposure, to facilitate the adjudication of compensation claims for cancers diagnosed following exposure to ionizing radiation. The 1985 working group did this by estimating "probability of causation" (PC) values, defined as

$$PC = \frac{\text{Risk due to radiation exposure}}{\text{Baseline risk + risk due to radiation exposure}}$$

for hypothetical instances of cancer following specific histories of radiation exposure. The report has been used mostly by the Department of Veterans Affairs (VA) as a guide to adjudicating compensation claims for cancers diagnosed in persons who were exposed during military service. The amount of new information about radiation-related cancer risk has increased markedly during the 15 years since publication of the report, and there have been revisions in the system of dose reconstruction used for the major source of epidemiological data for estimating risk, the cohort of atomic bomb survivors studied by the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. The VA requested the Secretary of the Department of Health and Human Services (DHHS) to update the Report, as provided for in the original legislative mandate, and joined with the DHHS to support the present effort by a working group of the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC).

Noting that the National Academy of Science/National Research Council (NAS/NRC) Committee on Biological Effects of Ionizing Radiation (BEIR VII, phase 2) is expected to complete within 2 or 3 years a comprehensive survey of the scientific data linking radiation exposure to health effects in human beings, the NCI and CDC have undertaken to provide an interim update of the 1985 report based on statistical analyses by the working group of readily available data on cancer risk following radiation exposure, notably the 1958-87 LSS Tumor Registry data on survivors of the atomic bombings of Hiroshima and Nagasaki made available on computer disk by RERF. It is expected that a further update to the present report will be made following the BEIR VII review. The working group has replaced the tabular format of the 1985 report by an interactive computer program (IREP, for "interactive radio-epidemiological program") that eliminates nearly all of the computational labor of estimating PC values and their uncertainties, and permits a more detailed and comprehensive expression of the various components of the calculation and their uncertainties.

It has been argued, notably by the NAS/NRC oversight committee that provided critical advice to the 1985 NIH working group (NAS, 1984), that the PC values calculated according to the formula given at the beginning of this summary pertain to populations rather than individuals, and that they "are not probabilities in the usual sense and are truly properties of the group to

which a person belongs, but in practice are assigned to the person for purposes of compensation." The oversight committee recommended a change in terminology, replacing "probability of causation," by "assigned share" (AS) to emphasize the difference. The NIH working group did not disagree, but continued to use "PC" because the term was already in common use. The present working group feels that the oversight committee's point is worth repeating, and has chosen to use "AS" throughout its report although "PC" is probably even more commonly used than in 1985. More generally, the working group emphasizes that the AS values obtained using the report and its computer program represent a summary of scientific findings about cancer risk following radiation exposure, that may be relevant to adjudication of individual claims, but that the report makes no claims regarding the influence of individual factors that have not been extensively studied.

It has also been argued by Greenland and others (Greenland, 1988, 1999; Robins, 1989a, 1989b; Beyea, 1999) that AS is a logically flawed concept, subject to substantial bias and therefore unsuitable as a guide to adjudication of compensation claims in cases of possibly radiation-related cancer. The argument is based largely on the possibility that radiation exposure may accelerate the time of appearance of cancers that, in the absence of exposure, would have occurred later. The conclusion of the present working group is that the argument may have theoretical merit but, as a practical matter, is unpersuasive in the light of current information about radiation-related risk. Scientific consensus about cancer risk following radiation exposure is constantly evolving as new information is uncovered. This is a time of rapid developments in our understanding of the carcinogenic process, and future developments may force a fundamental changes in our view of radiation carcinogenesis. For the present, however, the working group feels that current models are relevant both to radiation protection and the adjudication of claims for possibly radiation-related instances of cancer. Similar conclusions about the arguments of Greenland and others were reached by a an NAS/NRC subcommittee specially formed to review an earlier draft of the present report (NAS/NRC, 2000).

The focus of this report is on quantitative expression of uncertainty in AS, reflecting statistical uncertainty about risk estimates and more subjective uncertainty about model assumptions necessary to apply such estimates to the adjudication of compensation claims for cancer diagnosed following radiation exposure in the United States. In the U.S., unlike the United Kingdom where a voluntary "Compensation Scheme for Radiation-linked Diseases" allows for proportional compensation for AS values as low as 20% Wakeford, 1998), adjudication of claims revolves around the likelihood that AS may exceed 50%. When there is a policy bias ("benefit of the doubt") in favor of the claimant, focus is on upper credibility limits for AS rather than on a central estimate. For example, present VA policy is to award claims for which the upper 99% credibility limit for AS is 50% or higher.

Uncertainty, including the statistical uncertainty inherent in estimates obtained by fitting

observational data to theoretical models and subjective uncertainty inherent in model assumptions, is the primary focus of this report. One of the many advantages of replacing tables by an interactive computer program is that much more detail can be made easily available to the user, including a complete representation of the uncertainty pertaining to a particular AS estimate.

The 1985 NIH report dealt with 13 different cancer sites for which there was strong statistical evidence of a radiation dose response in human populations. However, lack of a statistically significant dose response for a particular cancer type does not preclude a compensation award based on an upper credibility limit for AS. For example, the upper 99% credibility limit for AS can be greater than 50% even if the radiation dose response is not statistically significant (or even if, in extreme cases, the point estimate is less than zero). The present report is based on the working assumption that any type of cancer can, in principle, be induced by radiation, and that the most important question concerns the magnitude of the risk associated with particular exposures. In all, 27 different cancers and groups of cancers are treated, including several cancer types not significantly associated with radiation dose. The report does not include malignant melanoma and chronic lymphocytic leukemia, for which adequate data were lacking. Lung cancer associated with radon exposure is given separately from that associated with external exposure. The radon-related estimates are based on an analysis using data from a 1996 report to the U.S. Department of Justice (DOJ 1996). A more comprehensive analysis, based on the most authoritative risk estimates published by the NAS/NRC BEIR VI Committee (NAS, 1999), was judged not to be easily adaptable for AS purposes and to require more computational and staff resources than those available to the present working group. Finally, this report, like the 1985 report, does not address the health consequences of *in utero* exposure to ionizing radiation.

Treatment of uncertainty in the updated report is guided by that in the original report and by more recent analyses, notably two publications of the National Council on Radiation Protection and Measurements (NCRP): Commentary 14 (NCRP, 1996), "A guide for uncertainty analysis and dose and risk assessments related to environmental contamination," and Report 126 (NCRP, 1997), "Uncertainties in fatal cancer risk estimates used in radiation protection." Essentially, the method involves calculation of an uncertain excess relative risk (ERR = excess risk/baseline risk) for the cancer of interest, as a function of radiation dose for each exposure. Other factors, represented by a series of randomly distributed factors which are assumed to be statistically independent, depend on informed but nevertheless subjective judgments from published reports of expert committees or by the authors of this report. They are designed to contribute bias correction and expression of additional uncertainty to a Monte Carlo simulation which provides a corrected ERR estimate, expressed as the product of all factors, and its uncertainty distribution combining all sources of uncertainty. If more than one exposure is involved, separate ERR values and uncertainty distributions are calculated for each exposure, and combined. The overall

ERR is then transformed to obtain the AS:

$$AS = ERR/(1+ERR).$$

Credibility limits for the AS are obtained as percentiles of its uncertainty distribution.

The various factors contributing to the overall estimate, and its uncertainty, are as follows:

ERR per unit of dose (or dose plus dose-squared) and its statistical uncertainty distribution are taken from the appropriate tabulated likelihood curve obtained as the final output of statistical model fitting performed by the working group. For most cancers, the ERR per unit of dose is allowed to depend on sex, age at exposure, and attained age (or, in the case of leukemia, time since exposure). The analysis specifically includes uncertainties in the parameters that quantify these dependencies. ERR per unit dose, as estimated, may be influenced by random and systematic errors in A-bomb survivor dosimetry, requiring several uncertain bias correction factors. Radiation dose for the claimant is entered by the user, either as a known value or as an uncertain value with a user-specified uncertainty distribution. Doses received at low doses and dose rates are adjusted by a factor (with uncertainty) known as the dose and dose rate effectiveness factor (DDREF), which may reduce the ERR per unit dose of gamma ray or other sparsely ionizing radiation. The DDREF does not apply to neutrons, alpha particles, or other kinds of densely ionizing radiation which are thought to have greater biological effects than sparsely ionizing radiation and are weighted accordingly. A separate term, the radiation effectiveness factor (REF), is used to express the differences in the biological effectiveness for various radiation types relative to the risk per unit dose induced by exposure to either acute or chronic exposures of high energy gamma radiation. As with the DDREF, uncertainty in the REF is expressed as a subjective probability distribution of possible values.

Site-specific baseline risks for many cancers differ substantially between Japanese and US populations, and there is considerable uncertainty about how this affects risks resulting from radiation exposure. An uncertain and complex factor is required for transfer of risk estimates from A-bomb survivors to a US population. Tobacco smoking is known to modify the carcinogenic effects of radiation to the lung, also requiring an uncertain adjustment factor. Finally, an optional uncertainty factor is included for additional, documented factors that may be justified as pertaining to identifiable subpopulations.

The present report is considered to be an interim update of the 1985 NIH report. Like that report, its AS estimates are based primarily on A-bomb survivor data. The present working group has had the advantage of access to comprehensive cancer incidence data from a greatly improved RERF Tumor Registry; these data are not only more recent than those used previously but are based on more timely and more accurate diagnoses than those available from death certificates. Incidence data are also more relevant to compensation claims for cancers of delayed or low

fatality. Direct access to RERF data allowed the working group to conduct its own analyses directed at the needs of this report, including modeling of dose-response modifiers such as age at exposure, and inclusion of cancer types not significantly associated with radiation exposure.

Unlike the 1985 report, the current report is based on linear dose-response models for all solid cancers, with an uncertain DDREF factor to allow for the possibility that risk per unit dose decreases with decreasing dose and dose rate. This approach is not necessarily better than the linear-quadratic model approach used previously, but it is in accord with recent recommendations by expert committees. Also, the present report treats relative biological effectiveness of densely cf. sparsely ionizing radiation as an uncertain quantity, relying on a report of the National Institute for Occupational Safety and Health. The present report's treatment of the problem of transfer of estimates between populations with different baseline rates is an important change, and accounts for a large part of the total uncertainty for several sites.

An early draft of this report was reviewed by a specially constituted subcommittee of the National Research Council's Committee on an Assessment of Centers for Disease Control and Prevention Radiation Studies from DOE Contractor Sites, namely, the Subcommittee to Review the Radioepidemiology Tables. That subcommittee, chaired by William J. Schull, released its report, entitled *"A Review of the Draft Report of the NCI-CDC Working Group to Revise the '1985 Radioepidemiology Tables,'"* on November 29, 2000 (NAS/NRC, 2000). As a result of that review, the Working Group has made a number of changes motivated by concerns expressed by the subcommittee about usability of the interactive computer program (IREP) by non-specialists, the omission of certain problematic cancer sites from the draft report, and inclusion of other sites for which the association between risk and radiation dose is not well established, e.g., because it is based on sparse data yielding very wide confidence bounds on dose-specific risk. The present report has also been influenced by recent legislation (Public Law 106-398: Energy Employees Occupational Illness Compensation Program Act of 2000) mandating the use of the 1985 NIH report, "as such tables may be updated from time to time under provisions of section 7(b)(3) of the Orphan Drug Act," for adjudicating claims related to cancers diagnosed in workers and former workers at Department of Energy facilities with histories of occupational exposure to ionizing radiation.

As previously mentioned, this is an interim report which is expected to be modified as new information on radiation-related risk becomes available. It is hoped that the *form* of the report may prove to be of more lasting value. In particular, the IREP program is constructed to allow - new risk estimates and statistical uncertainty distributions to replace old ones, for new cancer sites to be added, and for the treatment of other sources of uncertainty to be modified.

II. Background of 1985 report

A. Congressional mandate and its execution

On January 4, 1983 the President of the United States signed Public Law 97-414 (known as the "Orphan Drug Act"), an act to amend the Federal Food, Drug and Cosmetic Act to facilitate the development of drugs for rare diseases and conditions, and for other purposes. This legislation includes a provision (Section 7 (b) of the bill) directing the Secretary of Health and Human Services (DHHS) to "devise and publish radioepidemiological tables that estimate the likelihood that persons who have or have had any of the radiation-related cancers and who have received specific doses prior to the onset of such disease developed cancer as a result of these doses." The mandate included a provision for periodic updating of the tables.

It may be noted that the section of P.L. 97-414 pertaining to the development of radioepidemiological tables originally was introduced by Senator Orrin Hatch (Utah) as a part of Senate bill S 1483: "Radiation Exposure Compensation Act" to provide for damages due to radiation exposure from nuclear weapons tests in Nevada. Since neither this bill nor the companion House bill (H.R. 6052) was reported out of the respective committees, the section relating to radioepidemiological tables was attached as an amendment to the "Orphan Drug Act" which was passed by both houses and signed into law on January 4, 1983. The complete text of section 7 (b) of the bill and an excerpt from President Reagan's statement, on the occasion of his signing the Orphan Drug Act, are given in Appendix A of the present report.

Lead responsibility for the implementation of the enacted charge was assigned to the National Institutes of Health (NIH) by the Assistant Secretary of Health, DHHS, who also requested that a National Research Council (NRC) committee be formed to review the recommendations of the NIH. Subsequently (August 4, 1983), the Secretary of Health and Human Services approved the Charter for an "Ad Hoc Working Group to Develop Radioepidemiological Tables" to carry out this mandate. The text of the Charter is included as Appendix B.

An Ad Hoc Working Group, chaired by Dr. J. E. Rall, Deputy Director for Intramural Research, NIH, was established to carry out the work. The NIH contracted with the National Academy of Sciences (NAS) for the formation of an Oversight Committee in the NRC's Commission on Life Sciences, with the cooperation of the Institute of Medicine. The oversight committee, chaired by Prof. Frederick Mosteller of Harvard University, reviewed the data sources, assumptions, and methods of the NIH working group, and discussed wider issues regarding the tables in the context of their intended and possible uses. The report of the oversight committee was published in 1984 and the report of the working group was published on January 4, 1985.

Subsequent to the 1985 publication, the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) published a report on "Use of Probability of Causation by the

Veterans Administration in the Adjudication of Claims of Injury Due to Exposure to Ionizing Radiation" (CIRRPC 1988). The CIRRPC report expanded on the uncertainty evaluation in the 1985 NIH report, and provided doses for screening claims, which have subsequently been used by the Veterans Administration.

B. "Assigned share"

The National Academy of Sciences committee charged with oversight of the 1985 NIH radioepidemiological tables report (NRC, 1984) objected to the use of the term "probability of causation," or "PC," for the ratio,

$$PC = \frac{\text{risk due to radiation exposure}}{\text{baseline risk} + \text{risk due to radiation exposure}}$$

$$= \frac{\text{excess relative risk}}{1 + \text{excess relative risk}}.$$

The NAS committee pointed out that a negative ERR would result in a negative "probability" (a defect easily remedied by specifying boundary conditions for PC) and, more seriously, that the ratio applied to populations and not individuals and could not be interpreted as the probability that a given cancer was caused by a given radiation exposure. They recommended using the term "assigned share" as a more appropriate term, because the computed quantities "are not probabilities in the usual sense and are truly properties of the group to which a person belongs, but in practice are assigned to the person for purposes of compensation." The present working group is sympathetic to this view and is in large part guided by it.

C. Methodology used in the 1985 report

1. Data sources. Baseline rates were taken from U.S. cancer incidence data for 1973-81 (SEER, 1984), by sex but not by race, and averaged over time . Site-specific average excess rates were taken from the 1980 report of the NAS/NRC Committee on the Biological Effects of Ionizing Radiation (BEIR III) (NAS, 1980, Tables V-14 and V-16) and from other sources, as shown in Table II.C.1. Lymphoma, multiple myeloma, and cancers of the prostate gland, uterus and cervix, testis, and brain specifically were not covered, because of insufficient information and lack of a statistically significant dose response. Chronic lymphocytic leukemia (CLL) was considered to be unrelated to radiation exposure.

2. Dose-response models. Based on a review of the experimental and epidemiological literature, a specific linear-quadratic model was assumed for all of the sites tabulated above, with the exception of breast and thyroid gland, for which linearity was assumed. The linear-quadratic model for a single, acute exposure to sparsely ionizing radiation (low-LET, for low linear energy transfer) was that preferred by the BEIR III committee (NAS 1980, equation V-10),

$$\text{excess risk} = \alpha\,(D + D^2/1.16),$$

where D is dose in Gy and α depends upon site, age at exposure, and sex. The value of α was equal to the corresponding linear-model risk coefficient from BEIR III or other source, divided by 2.5. Excess risk associated with a chronic exposure, or with exposure to densely ionizing (high-LET) radiation, was assumed to be linear in dose, with coefficient α. Different exposures were considered to be additive in effect; that is, excess risks associated with radiation exposures at different times were calculated separately and summed.

3. Minimal latent period and distribution of risk over time following exposure. For leukemia and bone cancer, radiation-related risk was assumed to be distributed lognormally over time following exposure, with a minimal latent period of 2 years. The lognormal distributions differed by cancer type and subtype and (for acute leukemia) by age at exposure, and were obtained by fitting original data. For other cancers, excess risk was assumed to be proportional to age-specific baseline risk (i.e., ERR was assumed to be constant) beginning 10 years after exposure; it was further assumed that there was no risk up to 5 years following exposure, and that ERR increased from zero at 5 years to its full value at 10 years according to a symmetric, S-shaped cubic polynomial function of time.

4. Dependence of excess risk on sex and on age at exposure. Following BEIR III, risk estimates were given separately by sex and age at exposure categories, regardless of statistical significance for these factors. Original estimates were in the form of excess (absolute) risk per unit dose, by sex and interval of age at exposure, averaged over a follow-up time of 5-26, 10-30, 10-33, 10-34, or 10-35 years, depending upon site; this corresponded to the data sets on which the estimates were based. Original estimates were converted to dose-specific ERR by dividing estimated excess risk by baseline risk, i.e., obtained as the lifetable-weighted average of age-specific SEER rates (SEER, 1984) over the same follow-up period. Thus, for sites where the excess risk estimate was based on Japanese A-bomb survivor data, and where U.S. and Japanese baseline rates differ, it was assumed that absolute risks, and not relative risks, averaged over the period of observation, were the same in the two populations.

5. Modification of ERR by other exposures and/or by host factors. The question of host factor modification was not addressed explicitly. Modification by other exposures was discussed generally, but specific recommendations were made only for tobacco smoking, in the case of lung cancer, and for radiation exposures other than those at issue. Different radiation exposures were treated as additive in effect, as discussed in II.C.1 above. Thus, the excess cancer rate corresponding to a second exposure was assumed to be independent of the excess cancer rate corresponding to an earlier exposure. Smoking and low-LET radiation were also considered to be additive in effect with respect to lung cancer causation, that is, the radiation-related excess rate was assumed to be independent of smoking history. Thus, a smoker would have a lower

excess relative risk associated with exposure than an otherwise similar nonsmoker, because the nonsmoker's baseline rate was smaller. However, smoking and alpha radiation from inhaled radon decay products were considered to be multiplicative in effect, i.e., computation of ERR for radon exposure did not depend upon smoking history, since excess risk due to radiation and baseline risk were assumed to be proportionally affected by smoking history.

D. Uncertainty

Sources of biased and unbiased uncertainties, and propagation of errors, were extensively discussed in Chapter VII of the 1985 report. Biased uncertainties included overestimation of (absolute) risk 5-14 years following exposure, and underestimation associated with use by the BEIR III committee (NAS, 1980) of the T65D dosimetry system (Kerr,1979) for estimating dose-specific risk among A-bomb survivors. (By 1983-84 it was clear that T65D was going to be replaced, but the new system, DS86 (Roesch, 1987), was not yet in place.) Unbiased uncertainty pertained to the use of baseline rates based on the entire region covered by the SEER registry, modeling of risk as a function of age at exposure, assumptions about dependence of risk on time following exposure, and assumptions about the curvature of the linear-quadratic dose-response curve estimated in BEIR III. Other sources of uncertainty were also discussed, but only those just noted were taken into account in computing combined uncertainty, represented by a geometric standard deviation value and a bias correction factor, for different cancer sites and years following exposure. The emphasis of the report was on point estimates; recommendations were given for modifying tabulated AS values to account for bias and uncertainty.

CIRRPC (1988) also evaluated uncertainties in the PCs estimated in the 1985 publication. This assessment treated most uncertainties in the same way as the 1985 report, except that an evaluation of statistical uncertainty was added, uncertainty in evaluating age at exposure was increased, and additional probability was assigned to a linear dose-response.

The CIRRPC assessment was addressed primarily at providing doses for screening claims, and for this purpose, it was assumed that the claimant had a baseline risk at the 10^{th} percentile of the distribution of the baseline risks for the cancer of interest among all counties of the United States. Neither the 1985 publication nor CIRRPC evaluated uncertainty resulting from the use of the additive model for transferring risks from A-bomb survivors to the US population.

III. Reasons for update

A. New data, new findings

The original NIH report (NIH, 1985) was written in 1984, and based on data available at that time. Site-specific estimates of excess absolute risk (excess cases per 10^6 persons per year per rad), by interval of age at exposure, were obtained from the BEIR III report (NAS, 1980), which relied largely on A-bomb survivor mortality data for 1950-74 but also on other studies. The NIH report also used more recent risk coefficients from the A-bomb survivor Life Span Study (LSS) mortality report for 1950-78 (Kato and Schull, 1982) and site-specific, incidence-based studies of leukemia (Ichimaru, 1978), thyroid cancer (Parker, 1974, Ishimaru, personal communication), and preliminary data on female breast cancer (Tokunaga, 1987) in the same population. To a lesser extent, the report surveyed studies of cancer mortality in British patients given therapeutic radiation for ankylosing spondylitis (Smith and Doll, 1982), lung cancer among Czech, Canadian, Swedish and U.S. uranium miners (Jacobi et al, 1985), thyroid cancer in patients given x-ray epilation for treatment of tinea capitis (Ron and Modan, 1980), breast cancer among women given medical x rays (Boice, 1977, Shore, 1977), bone sarcoma among German patients treated for benign disease with injected radium (Mays, 1983), and estimates of salivary gland cancer risk in various irradiated populations (Land, 1986).

In the succeeding 15 years, the dose reconstruction system for the A-bomb survivors has been revised, and a large amount of new information has been obtained relating radiation exposure to subsequent cancer risk. For example, the number of cancer deaths among members of the cohort of atomic bomb survivors followed by the RERF in Japan increased from 3842 in 1950-74 (Kato and Schull, 1982) to 7827 in 1950-90 (Pierce et al, 1996). Much of the newer information pertains to cohort members exposed during the first and second decades of life: as these survivors reached ages at which cancer rates normally become appreciable, the newer data supported statistically stable risk estimates not obtainable previously. The same is in general true for other exposed cohorts that include persons exposed at young ages. In the original NIH report it was possible to estimate risk of radiation-related cancer following exposure before age 10 and at ages 10-19 for leukemia and cancers of the female breast, salivary gland, thyroid gland, and bone, while lung and stomach cancer risk estimates were available for exposure at ages 10-19. For other sites covered by the report (esophagus, colon, liver, pancreas, and urinary cancers), no calculations were done for exposure ages less than 20.

In addition, national and international committees have evaluated the newer data and used them for risk assessment (NAS/NRC, 1990, ICRP, 1991, UNSCEAR, 1988, 1994). Although none of these evaluations take account of the latest data, they are based on more recent data than BEIR III and their existence and current use for radiation protection purposes underscores the fact that the estimates used in the 1985 NIH report are out of date. The risk estimates provided in ICRP

Report 60 (1991) (based on the UNSCEAR 1988 report), in particular, are widely used and are generally higher than those in the BEIR III report.

B. New availability of risk data at the level of incidence.

Perhaps the most important recent development, however, has been a remarkable improvement, by the Radiation Effects Research Foundation (RERF) and its collaborators in Hiroshima and Nagasaki, of the Life Span Study (LSS) Tumor Registry to a high level of accuracy and efficiency (Mabuchi, 1994). The LSS registry draws on hospital records and physician notifications accessed by the local tumor registries of Hiroshima City, Nagasaki City, and Nagasaki prefecture, pathology and hematology records through the Hiroshima and Nagasaki tissue registries, and the Leukemia Registry developed in the late 1940s and early 1950s, as well as the virtually complete system of mortality notification and ascertainment of death certificate diagnosis that is the basis of the LSS mortality studies of atomic bomb survivors. In general, incidence data, when they can be obtained, are superior to mortality data because they capture information on cancers of low or delayed fatality and because they are based on diagnostic information that is more detailed and more accurate than death certificate data.

C. The use of the NIH report today is somewhat different from that contemplated at the time the report was written.

The circumstances of the legislation mandating the 1985 NIH report suggested that partial compensation for claims of radiation-related cancer might be made on the basis of assigned share estimates between 10% and 50%, whereas full compensation would apply for AS ≥ 50%. Thus, the main graphical displays in the report show computed, "best-estimate" AS values corresponding to organ doses of 1, 10, and 100 rad (0.01, 0.10, and 1.0 Gy), as a function of age at exposure and/or time following exposure, and the reader is referred to the chapter on uncertainty limits for instructions on how to compute them. In fact, the tort law concept of "at least as likely as not," corresponding to AS ≥ 50%, continues to dominate the language of claim adjudication, with the notable modification in some important applications that claims may be winnowed out only if there is little or no reasonable doubt that the true value of the AS is less than 50%. For example, the Department of Veterans Affairs (DVA) screens out claims for which the 99% upper limit for the AS is less than 50% (Dr. Neil Otchin, personal communication). This development suggests that any revision of the 1985 report should seek a more nearly complete expression of the scientific information related to risk of cancer following exposure to ionizing radiation, as it applies to particular cases. In other words, emphasis should be placed upon a comprehensive expression of uncertainty, and one that is easily accessible to the user.

At a fairly late stage in its development, the present report was overtaken by events in the form of the Energy Employees Occupational Illness Compensation Program Act (EEOICPA) of 2000 (Public Law 106-398). That law established new programs for assisting nuclear weapons

production employees who have work-related illnesses. These programs include a federal program, administered by the U.S. Department of Labor (DOL), for eligible employees with chronic beryllium disease, silicosis, and possible radiation-related cancers. The act requires that adjudication of claims for radiation-related cancers be based on the radiation dose received by the claimant (or a group of employees performing similar work) at such facility, and on a determination that a probability of causation (assigned share) value of 50% or greater is consistent with the appropriate upper 99 percent confidence limit in the radioepidemiological tables published by the NIH in 1985, "as such tables may be updated from time to time under provisions of section 7(b)(3) of the Orphan Drug Act." Thus, the decision rule used by the DVA to screen (and, in practice, to award) claims has now been accorded the force of law.

The CDC's National Institute of Occupational Safety and Health (NIOSH) has been charged with (1) providing information to the DOL on estimated radiation doses for claimants' past occupational exposures to radiation, in cases where exposure measurements are unavailable, incomplete, or of poor quality (dose reconstruction), and (2) providing advice on the scientific guidelines that DOL would use in determining whether it is at least as likely as not that an energy employee's cancer was caused by occupational exposure to radiation (determining the assigned share or probability of causation). The NCI-NIH working group, while working to respond to the recommendations of the NAS-NRC review committee, has had the benefit of discussions with members of the NIOSH Office of Compensation Analysis and Support. Mindful of its responsibilities under the EEOICPA of 2000, the NIOSH group made a number of suggestions for the revised report to address specific NIOSH requirements. These suggestions, and the working group's responses, are discussed in the body of the present report.

D. New attention to cancer sites whose association with radiation exposure is tenuous.

The cancers covered by the 1985 NIH report were those for which a statistically significant radiation dose response had been demonstrated in one or more major analyses. Statistical significance is equivalent to having a positive lower confidence limit, at a certain confidence level, for dose-specific excess relative risk, and therefore also for the AS. The list of cancers fitting this criterion is not greatly different today, but it is clearly possible for an upper uncertainty limit for the ERR to be greater than 1, and hence for the corresponding AS limit to be greater than 50%, even when the estimated ERR is not significantly greater than zero. Thus a wider range of cancer sites is of interest than that covered by the 1985 report.

E. New analytical approaches and ways of summarizing data

The 16 years since the 1985 NIH report have seen enormous advances in accessible computing power, particularly at the level of personal computers, and the development and refinement of statistical packages for risk analysis. An important consequence is that statistical modeling of radiation dose response and its modification by factors such as gender, age at exposure, time

since exposure, age at observation for risk, smoking history, and reproductive history can be carried out far more quickly and easily than before. New analyses, tailored for particular applications like the subject of this report, are easily accomplished, especially since the most comprehensive LSS mortality and incidence data are available from the RERF web site, at http://www.rerf.or.jp. These data, grouped to protect the privacy of individual survivors, are those used in the 1950-90 mortality report (Pierce et al, 1996) and the cancer incidence reports based on RERF Tumor Registry and Leukemia Registry data through 1987 (Thompson et al, 1994, Preston et al, 1994). The AMFIT algorithm for Poisson model regression, part of the Epicure statistical package (Preston et al, 1991), is particularly well suited for cohort-based analyses of radiation-related risk and has become closely identified with analyses of A-bomb survivor data in particular. These statistical approaches were used, for example, to develop the models used in the BEIR IV, V, and VI reports (NAS, 1988, 1990, 1999).

F. More attention to uncertainty and presentation of risk

The 1985 NIH report presented illustrative graphs of assigned share estimates, tables of coefficients for various components needed to compute assigned share, and algorithms for calculating assigned share from these coefficients for arbitrary values of radiation dose, age at exposure, and time following exposure. Statistical and other sources of bias and uncertainty were extensively discussed in a separate chapter, and estimates and algorithms were provided for calculating "credibility limits" (based on statistical and subjective measures of uncertainty) for estimates of assigned share. In the intervening years, additional attention has been paid to quantification of uncertainty in applications to radiation-related risk, and new approaches for evaluating uncertainty have been developed (NAS, 1990, NCRP, 1996, 1997, EPA, 1999). It seems clear that considerations of uncertainty are central to radiation protection and adjudication of claims for compensation in cases of disease following radiation exposure. It is equally clear that the concept is complex and not easily applied by non-specialists, and would benefit from a more user-friendly approach as indicated by the following example:

The major U.S. government user of the NIH report to date is the Department of Veterans Affairs (DVA) which in 1985 asked the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) of the Office of Science and Technology Policy, Executive Office of the President, to provide guidelines on how the NIH report might be used credibly to assist in adjudicating a veteran's claim of radiation injury. The Science Panel of CIRRPC interpreted the DVA's charge as one of quantifying the likelihood that a specified "probability of causation" (assigned share) in the NIH report would not be exceeded, with an *a priori* chosen level of credibility (CIRRPC, 1988). Their solution was to tabulate, by type of cancer, gender, age at exposure, and other relevant factors, the organ doses at which the upper AS credibility limit was 50% ("as likely as not") at credibility levels 90%, 95%, and 99%, respectively. The solutions were proposed as possible screening doses for specific cancers, exposure ages and times

following exposure. The screening procedure was biased toward ensuring that a marginal claim by an exposed veteran would not be rejected at this stage of consideration, and it was assumed that a claim not eliminated by this screening process would be adjudicated on its merits, taking into consideration the many factors that pertain to an individual claimant, including the AS value calculated according to the NIH report.

G. Availability of interactive computer programs as an alternative to tabular presentation

The tabular presentation of the 1985 report allowed users to look up tabulated coefficients appropriate to particular claims, and to calculate assigned share using these coefficients according to simple algorithms presented in the report. Increased computing power has made it possible to calculate assigned share and its uncertainty directly, for individual claims, from the particulars of exposure history, disease, and other relevant factors. This results in quicker, easier, and less error-prone computation, with tabular and/or graphical output options.

H. Use of organ-specific equivalent dose, in sievert (Sv)

The present report expresses organ-specific radiation dose in gray (1 Gy = 1 joule of energy per kilogram of tissue), instead of the quantity used in the 1985 report, the rad (1 Gy = 100 rad; equivalently, 1 cGy = 1 rad). The report expresses equivalent dose, which incorporates weighting factors to represent the biological effectiveness of different types and energies of radiations, in sievert (1 Sv = 100 rem, where the rem is the quantity used previously). For irradiation by high-energy photons, such as exposure to gamma rays from the atomic bombings of Hiroshima and Nagasaki, the biological effectiveness is taken to be unity, by definition, and dose and equivalent dose are numerically the same (e.g., 5 cGy = 5 cSv). However, for alpha particles, neutrons, and lower-energy photons and electrons, a given dose is assumed to correspond to a higher equivalent dose, and the relationship between equivalent dose and dose depends on the radiation type and sometimes its energy and dose level.

In the present report, it is assumed that the starting point for calculation of AS is a single value or set of values of tissue-specific equivalent dose expressed in Sv, and that equivalent dose was calculated from an estimated dose (Gy) in the tissue of concern using standard conversion factors (average quality factors or radiation weighting factors) developed for radiation protection purposes. The estimated tissue dose from each radiation type obtained using the standard conversion factor then is modified by a radiation effectiveness factor (REF) for that radiation type and energy to give an equivalent dose in Sv and its uncertainty for use in calculating AS. This equivalent dose differs from the value used as the starting point in that the REF is expressed as a probability distribution based on radiobiological data (Kocher et al., 2002), rather than a point value of a standard quality factor or radiation weighting factor used in radiation protection. Thus, the calculation of AS specifically takes account of the biological effectiveness of each radiation type and energy of concern and its uncertainty.

IV. Description of the Approach

A. Overview

1. Assigned Share

Assigned share (AS) for an individual who was exposed to radiation, and who has been diagnosed with a cancer thought to be related to such exposure, is given by

$$AS = ERR/(1 + ERR)$$

where ERR is the excess relative risk associated with the exposure(s) of interest. ERR is a function of radiation dose (possibly accumulated over a number of exposures), age(s) at exposure, type of cancer, age at diagnosis, gender, and other factors possibly related to baseline and/or radiation-related risk.

As previously mentioned (section II.B), the working group is sympathetic to the view expressed by the 1984 oversight committee report (NAS, 1984), that the ratio, called "probability of causation," or "assigned share" (which we prefer) applies to populations and not individuals and cannot, for lack of detailed information and the ability to understand its full implications, be interpreted as the probability that a given cancer was caused by a given radiation exposure. The working group views assigned share as an actuarial concept, useful for summarizing the existing scientific evidence bearing on the likelihood that prior radiation exposure might be causally related to cancer occurrence under various circumstances, and which may in fact be the best available information pertaining to a particular case. Similarly, a statistical life table is a useful device on which to base social contracts such as a life insurance contract. A life table is based on observed frequencies of deaths by age in a large population and, with detailed information, it is easy to define, and easier still to imagine, subgroups for which life-table predictions based on the larger population may perform poorly. Yet these departures do not detract from the practicability of basing decisions about annuities, insurability, and insurance rates on life table predictions in the absence of such detailed information.

2. Sources of uncertainty

New emphasis is placed on uncertainty analysis (NCRP, 1996), specifically, estimating an uncertainty distribution for the ERR (and associated AS), as opposed to a single point estimate. ERR is expressed as the product of several factors, which are assumed to be statistically independent. Each factor is uncertain, and is specified by an uncertainty distribution. The specified uncertainty distributions depend to some extent on subjective judgments by expert committees and by the authors of this report. The overall uncertainty distribution of the desired ERR is obtained by Monte Carlo simulation. These simulations involve sampling from the uncertainty distributions for each of the factors (or sources) included, and are similar to those

conducted by the Environmental Protection Agency (EPA,1999) and the National Council on Radiation Protection and Measurement (NCRP,1997). A computer program, here called IREP (for interactive radio-epidemiological program), has been developed to conduct these simulations individually for any desired application, taking account of specific characteristics of both the exposure and of the exposed individual.

The sources of uncertainty that are included are listed below, with details given in the sections that follow and in the appendices.

1. Sampling variability in the estimated ERRs. Statistical analyses of A-bomb survivor cancer incidence data were performed to estimate the ERR and its associated statistical uncertainty for each type of cancer. Dose response was assumed to be linear for solid cancers, after dose-response analyses found no evidence of departure from linearity. For leukemia, dose response was assumed to be linear for densely ionizing radiation such as neutrons and alpha particles, and for sparsely ionizing radiation (e.g., gamma ray, x ray) delivered at low dose rates; but quadratic for acute exposures to sparsely ionizing radiation. For most cancer types, the dose response was allowed to depend on sex, age at exposure, and age at diagnosis. Sampling variability includes both uncertainty in the overall risk estimate and in estimated parameters that quantify these dependencies. Details are given in Section IV.D and Appendices C and D.

2. Correction for random and systematic errors in A-bomb survivor dosimetry. The statistical uncertainty discussed in the preceding paragraph pertains to assigned share for a member of the LSS sample, or for another A-bomb survivor whose radiation dose was estimated by the same methodology. It would not pertain exactly to another irradiated population with identical baseline cancer rates, because any biased or unbiased uncertainties in the reconstructed radiation dose estimates for the A-bomb survivors would not apply to the second population. Thus, risk estimates are adjusted for random errors in the doses assigned to individual A-bomb survivors, and also to several potential sources of systematic bias in these doses. The latter include systematic underestimation of gamma rays for Hiroshima survivors, uncertainty in the weighting factor for neutrons, and uncertainty in the neutron component of the total dose. Details are given in section IV.E and Appendix D.

3. Extrapolation of risk from sparsely ionizing radiation to low doses and dose rates. Doses received at low doses and dose rates are adjusted by a factor known as the Dose and Dose Rate Effectiveness Factor (DDREF). The treatment of the uncertainty in this factor is described in Section IV.F and Appendix D.

4. Transfer of risk estimates to a US population. Baseline risks for many cancers differ substantially for Japanese and US populations, and there is considerable uncertainty about how risk estimates derived from observations on an exposed Japanese population should be applied to an exposed US population. The treatment of this source of uncertainty is described in Section

IV.G and Appendix D.

5. Biological effectiveness of different radiations. Densely ionizing radiation, with a high energy transfer per track length in tissue (high linear energy transfer, LET), such as protons, neutrons, and alpha particles and other heavy ions, generally has a greater biological effectiveness per unit dose than low-LET radiation, such as gamma rays, x rays, and beta particles. For radiation protection purposes, dose of high-LET radiation in Gy is weighted by a factor, called the radiation weighting factor (w_R), which depends on the type of radiation and sometimes its energy (ICRP, 1991). The resulting weighted dose, called equivalent dose, is in Sv and provides a common metric of biologically significant dose for all radiation types. There is no uncertainty about w_R, since it is a defined value for a particular radiation type for use in radiation protection. For purposes of estimating risk and AS, however, w_R may be only a rough approximation of the biological effectiveness, relative to low-LET radiation, which is required when risk coefficients derived from studies of populations exposed mainly to low-LET radiation are applied in cases of exposure to high-LET radiation. In addition, the biological effectiveness of low-LET radiations (photons and electrons) may depend on energy, and this is not normally taken into account in radiation protection. Thus, biological effectiveness generally depends on the radiation type, and sometimes its energy and level of dose, and is an uncertain quantity. Treatment of uncertainties in biological effectiveness of different radiation types based on uncertainties in radiobiological data, which is discussed in Section IV.H, relies on a separate report commissioned by NIOSH (Kocher et al., 2002).

6. Modification by smoking history. Tobacco smoking and, to a lesser extent, exposure of nonsmokers to side-stream tobacco smoke are powerful risk factors for lung cancer, especially, and a number of other cancers as well. Studies of uranium miners suggest that risk of radiation-induced lung cancer is increased among smokers to a greater extent than among non-smokers, but that this increase is somewhat less than the increase associated with smoking alone (NAS, 1999). The interaction between radiation exposure and smoking history is discussed in Section IV.I.

The following additional sources of uncertainty have been considered by others, but are not evaluated here.

1. Diagnostic misclassification in A-bomb survivor data. Both the NCRP (1997) and EPA (1999) uncertainty evaluations were based on mortality data, for which diagnostic misclassification is a more serious problem than for the incidence data used for this report. Also, the present report focuses on specific cancers, and diagnostic accuracy may depend on the cancer type. Although there is undoubtedly uncertainty resulting from diagnostic misclassification, it would be very difficult to quantify, and it does not seem likely that this uncertainty would be large relative to many of the other sources considered.

2. Extrapolation of risk beyond the time period covered by data. The focus of NCRP Report 126 (1997) was lifetime cancer mortality risk associated with radiation exposure, and the report specifically treated uncertainty about extrapolation of risk beyond the period of observation for risk. The concern was that the A-bomb survivor mortality data for 1950-1985 represented follow-up only until 40 years after exposure, whereas those data were being used to estimate lifetime risk for persons exposed at various ages including children whose expected remaining lifetime when exposed was 50, 60, 70, or more years. The NCRP report included a factor whose uncertainty contributed 6.7% of the overall uncertainty to *lifetime* mortality risk for a population of all ages at exposure, and 0.5% for a working population 20-65 years of age at exposure.

The present report is subject to the same problems of projection of risk beyond the period of observation, even though the vast majority of claims for which the report might be relevant are expected to pertain to adult exposures, for which such projection contributes little compared to other sources of uncertainty. However, (uncertain) trends in time since exposure (leukemia) or attained age (solid cancers), which address some of the same issues, were specifically included in the set of variables used to model radiation-related risk for different kinds of cancer, and were retained in the model as appropriate on statistical grounds.

B. Sources of data

Although much new information on radiation-related risk in human populations has been published in the 15 years since the 1985 NIH report was prepared, the present report relies primarily on analyses by the Working Group of A-bomb survivor incidence data. The approach involved direct calculation of risk estimates and their statistical uncertainties from original data, in this case from the RERF Tumor Registry for 1958-87 (Thompson et al, 1994) and the RERF Leukemia Registry for 1950-1987 (Preston et al, 1994). Thyroid cancer received a more widely-based approach, involving a new analysis of the original thyroid cancer data from the international, pooled study of Ron et al (1995). Radon-related lung cancer risk estimates were computed by the Working Group using data and statistical models consistent with those used for a Department of Justice report (DOJ, 1996). Dale Preston, Chief of Statistics at the RERF, provided estimates for non-melanoma skin cancer based on the original data from a published study (Ron et al, 1998).

C. Choice of cancer types and approach to cancer types.

Adjudication of compensation claims for possibly radiation-related cancer is usually specific to organ site and often to histological type, and for this reason, models need to be developed for estimating risks for cancer of specific sites. Sites for solid tumor incidence data from the RERF Tumor Registry, as tabulated by Thompson et al (1994), are reproduced in Table IV.C.1, and sites for hematopoietic cancers from the Leukemia Registry, as tabulated by Preston et al (1994) are reproduced in Table IV.C.2. The final column of each table indicates grouping and other

treatment of each site for the present report. Estimates of the ERR per unit of exposure for site-specific cancers are often imprecise, especially for less common cancers. The need to estimate parameters that allow for modification of risk by sex, age at exposure, and attained age adds to the difficulty. In the approach described below, we have tried to strike a balance between allowing for differences among cancer sites and statistical precision.

For solid cancers, the general approach to defining categories was to provide separate estimates for each cancer site represented in the LSS data set by 50 or more cases among A-bomb survivors exposed to >5 mSv. Categories (with their ICD codes) that met this criterion were oral cavity and pharynx (140-141), esophagus (150), stomach (151), colon (153), rectum (154), liver (155.0), gallbladder (155.1, 156), pancreas (157), lung (162), female breast (174), uterine cervix (180), ovary (183), prostate (185), bladder (188), and nervous system (191,192). Thyroid cancer (193) and non-melanoma skin cancer (173) also met this criterion but for those sites more extensive data from Ron et al. (1995), and Ron et al. (1998) were used. To allow inclusion of additional categories that did not meet this criterion, uterine cervix was merged with other female genital cancers except ovary (179-182, 184), and prostate was merged with other male genital cancer (185-187). There was little or no evidence of dose-response for any of these cancers (Thompson et al, 1994). Additional categories for which estimates are provided are all digestive cancers (to be used for digestive cancers not included above, i.e. ICD codes 152, 158, 159); all respiratory cancers excluding lung (160-161, 163-165); all urinary cancers (to be used for kidney (189)); and a residual group of solid cancers (170-172, 174-males, 175, 190, 194, 195).

For hematopoietic cancers, estimates are provided for each category shown in Table IV.C.2, even though the number criterion used for inclusion of solid cancer sites was met only for the largest grouping of leukemia types. Chronic lymphocytic leukemia (CLL) was specifically excluded from the risk calculations because of a lack of data on which to base an estimate. CLL is almost absent among Japanese generally and among the A-bomb survivors in particular (Parkin, 1997, Preston, 1994), but occurs frequently in Western populations, especially at older ages (Parkin, 1997). It has not, however, been associated with radiation exposure in studies of irradiated Western populations (NAS, 1990). Lymphoma and multiple myeloma are grouped together and treated in a manner similar to that for solid cancers as discussed below.

Radon-related lung cancer, although included in the 1985 NIH report, was not covered by the initial version of the present report because adaptation of the BEIR VI report (NAS 1996) for this purpose was felt to be beyond the resources of the Working Group. Inclusion was recommended by the NRC review subcommittee, and by government agencies (notably NIOSH) likely to use the revised report to adjudicate compensation claims. It was pointed out by the NRC review subcommittee (NAS-NRC, 2000) that Appendix A of a 1996 report prepared for the Department of Justice (DOJ, 1996) contains tables of cumulative radon exposures, in working level months (wlm), consistent with point estimates and upper 80% and 90% confidence limits for probability of

causation greater than or equal to 50%. The original data set used for these calculations, restricted to exposures ≤ 3200 wlm, was used by the Working Group to model lung cancer risk as a function of cumulative radon exposure.

D. Estimation of risk coefficients and their statistical uncertainties

1. Solid cancers from the RERF tumor registry report data.

In the models described in this section, thyroid cancer and non-melanoma skin cancers are excluded, and the term "all solid cancers" is used throughout to indicate solid cancers (ICD 140-199) without these two cancers. Site-specific baseline risks were modeled by stratifying on gender, city of exposure (Hiroshima or Nagasaki), calendar time, and attained age using the general approach described by Pierce at al. (1996). The following linear dose-response function was used to model the ERR:

$$ERR(D,s,e,a) = \alpha D \exp[\beta I_s(sex) + \gamma f(e) + \delta g(a)]$$

or, equivalently for $\alpha>0$, (IV.D.1)

$$ERR(D,e,a) = D \exp[\log(\alpha) + \beta I_s(sex) + \gamma f(e) + \delta g(a)],$$

where D is dose in Sv, $I_s(sex)$ is an indicator function for the *opposite* sex (i.e., $I_s(sex) = 1$ for females and = 0 for males if s corresponds to "male", and conversely if s corresponds to "female"), e is age at exposure in years, a is attained age in years, f and g are specified functions of e and a, respectively, and α, β, γ, and δ are unknown parameters. The term $\beta I_s(sex)$ in expression (IV.D.1) is a computational convenience that allows the ratio between sex-specific estimates to be determined using site-nonspecific data, as discussed later. Based on published analyses of the RERF incidence data for 1958-87 with $f(e) = e$-30 and $g(a) = \log(a/50)$ (Thompson, 1994), it would not be necessary to include both age at exposure and attained age, for most sites, in a parsimonious model. However, it is our understanding that updated cancer incidence and mortality data, currently being evaluated at RERF, indicate a more general need for both variables (D. Preston, personal communication). In addition, the NAS/NRC review of an earlier draft of this report recommended models that allowed for attenuation of risk with time. The parameter δ in our general model (IV.D.1) allows for such attenuation.

The following specifications for the functions $f(e)$ and $g(a)$ were evaluated, and specification C was chosen for reasons discussed in the next paragraph.

A: $f(e) = e - 30,\ g(a) = \log(a/50)$;

B: $f(e) = min(e - 30, 0),\ g(a) = min(\log(a/50), 0)$;

C: $f(e) = min(max(-15, e - 30), 0),\ g(a) = min(\log(a/50), 0)$,

where "min" denotes "minimum" and "max" denotes "maximum".

The chosen specification (C) for $f(e)$ and $g(a)$ can also be written as follows:

$$f(e) = -15 \text{ for } e \le 15, = e - 30 \text{ for } e \text{ between } 15 \text{ and } 30, \text{ and } = 0 \text{ for } e > 30;$$

$$g(a) = \log(a/50) \text{ for } 0 < a < 50, \text{ and } = 0 \text{ for } a \ge 50. \qquad \text{(IV.D.2)}$$

When fitted to data for all solid cancers, the deviance values for models using the specifications A, B, and C were 3746.94, 3746.52, and 3743.15, respectively, with smaller deviance values indicating a closer fit of model to data. The nearly identical fits of models using A and B indicate that there is no direct evidence of modification of the ERR for exposure ages over 30 or attained ages over 50, and the somewhat better fit of model C indicates a lack of direct evidence of variation of the ERR by exposure age under 15. The model using C was chosen for application to solid cancers because it provided a better fit than the other two and because it allowed more statistically stable estimates at the extremes of exposure ages and attained ages. Exceptions were cancers of the thyroid gland and skin, as discussed at the end of section IV.D below. The chosen model, as fitted to the data, has the properties that, for fixed attained age, log(ERR/Sv) is constant (at different levels) for exposure ages less than 15 years and greater than 30, and decreases linearly with exposure age between 15 and 30. For fixed exposure age, log(ERR/Sv) decreases linearly with log(age) until age 50, and remains constant thereafter. With this choice of f and g, the parameter α represents (sex-specific) ERR/Sv for exposure age 30 or older and attained age 50 or older, since both f and g are zero for these ages. For exposure age e younger than 30 and/or attained age a younger than 50,

$$\text{ERR/Sv} = \alpha \times h(e, a; \gamma, \delta),$$

where

$$h(e, a; \gamma, \delta) = \exp\{\gamma f(e) + \delta g(a)\}$$

and where $f(e)$ and $g(a)$ are defined above according to specification C (IV.D.2).

The approach used to model parameters for site-specific cancers is similar to that used by Pierce and Preston (1993). With this approach, the parameters β, γ, δ, are estimated using data on all solid cancers, and these common values are then used for site-specific cancers unless there is evidence that the site-specific values differ significantly from the common values. In the application here, common values of the parameters γ and δ were used for all site-specific cancers with the exception of lung cancer and female genital cancers other than ovary. For lung cancer, a model with no age effects ($\gamma = \delta = 0$) provided a nearly identical fit to that obtained when both parameters were estimated, with some evidence of departure from the common values ($p = .12$ based on 2 d.f.) For female genital cancers other than ovary, a model with no age effects was also used; in this case, the estimated ERR/Sv was negative, and the fitted model would not

converge with the common age parameters. Although there was modest evidence that the attained age effects were stronger for nervous system cancers and the residual category of all other cancers, data for these sites were judged too sparse to support separate estimates. For all other sites, p-values testing the appropriateness of the common values exceeded 0.2.

The parameters for the main effects (α) were estimated using only data on the cancer site of interest with γ and δ set equal to their common values . For cancers of the stomach, colon, and lung, the gender effect (β) was also estimated in this manner. For liver cancer, it was assumed that the ERRs for the two sexes were the same ($\beta = 0$), a result supported by Cologne et al (1999). For all remaining non-sex-specific cancers, the gender parameter obtained in an analysis of all non-sex-specific solid cancers combined was used; this value was $\beta = 0.843$, which corresponds to a female/male ratio of 2.3. In no case was there evidence of significant departure from this common value.

To evaluate the uncertainty in the estimated ERR/Sv for each sex at the various exposure and attained ages, it was necessary to consider the uncertainties and dependencies among the estimated parameters α, β, γ, and δ. To accomplish this, an approach known as joint analyses (Pierce and Preston 1993) was used. This approach allows one to estimate some parameters that are common to two or more cancer sites, and other parameters that differ by site. It also allows one to evaluate the resulting uncertainties and correlations of the estimated parameters. In the applications used here, separate main effects were estimated for (1) the specific cancer (or group of cancers) of interest, and (2) all solid cancers excluding the specific cancer of interest. All data were used to estimate γ and δ. For cancer categories where the common gender effect was used, the second group was further subdivided into non sex-specific and sex-specific cancers; only non-sex-specific cancers were used to estimate β.

A possible approach for evaluating the uncertainty in the estimated ERR/Sv for each sex at various exposure and attained ages would have been to conduct joint analyses as described above, defining the parameters so that α reflected the ERR/Sv associated with a particular sex/exposure age/attained age, and obtain the profile likelihoods for the fitted α. However, this would have been extremely cumbersome (with slow computational speed) to implement in IREP, the interactive computer program for applying the algorithms developed by the working group.

In the interests of improving the computational speed of IREP, two approaches were used to estimate the unknown parameters α, γ, and δ and the statistical uncertainty distribution of ERR/Sv. In approach 1, the statistical uncertainty distribution was approximated by applying lognormal assumptions to the point estimates and covariance matrix for the three estimated parameters, $\log(\alpha)$, γ, and δ. This was done for five different site-sex combinations with relatively large numbers of cases and strong evidence of effects: all digestive cancers (male and female), stomach cancer (female), liver cancer (combined sexes), and female breast cancer.

These cancers contributed most strongly to the common estimates of γ and δ, and the correlations of $\log(\alpha)$ with γ and δ were therefore somewhat higher than for other sites. Also, the statistical likelihood distribution of ERR/Sv was closely approximated by a lognormal distribution. The means, variances, and covariances of the uncertainty distributions for the parameter estimates are shown in Table IV.D.1. For each of these site-sex combinations, the geometric mean (GM) and geometric standard deviation (GSD) of the statistical uncertainty distribution of ERR/Sv, evaluated at exposure age e and attained age a, are given by

$$GM = \alpha \times h(e, a; \gamma, \delta), \qquad \text{(IV.D.3)}$$

$$GSD = \exp\{[\mathrm{var}(\log(\alpha)) + \mathrm{cov}(\log(\alpha), \log(h(e, a; \gamma, \delta))) + \mathrm{var}(\log(h(e, a; \gamma, \delta)))]^{1/2}\},$$

where

$$\mathrm{cov}(\log(\alpha), \log(h(e, a; \gamma, \delta))) = \mathrm{cov}(\log(\alpha), \gamma) f(e) + \mathrm{cov}(\log(\alpha), \delta)\, g(a),$$

$$\mathrm{var}(\log(h(e, a; \gamma, \delta))) = \mathrm{var}(\gamma) f(e)^2 + 2\,\mathrm{cov}(\gamma, \delta) f(e) g(a) + \mathrm{var}(\delta) g(a)^2.$$

Approach 2 was used for all other solid cancer sites, with the exceptions of thyroid cancer and non-melanoma skin cancer for which the analyses were based on different data sets. For the sites treated using approach 2, correlations of $\log(\alpha)$ with γ and δ were not [illegible] (Appendix C), and it was considered appropriate to base the uncertainty evaluation on the assumption that α was independent of γ and δ. The fitting process was repeated, this time with parameters γ and δ set equal to the common values obtained from a fit for all solid cancers: $\gamma = -0.05255$ and $\delta = -1.626$. Thus, the site-specific and sex-specific dose effect α was estimated assuming no correlation of $\log(\alpha)$ with γ and δ. For non-sex-specific cancers, joint analyses were used with a common gender parameter (β) and separate main effects (α) for the cancer of interest and remaining non-sex-specific cancers. Inclusion of data for other, non-sex-specific solid cancers served to stabilize the male/female ratio of dose coefficients for males and females. Statistical uncertainty distributions for cancers treated using approach 2 are calculated in IREP by Monte Carlo simulation based on the statistical likelihood profile distribution for $\log(\alpha)$, given in Table IV.D.2 for most sites for which approach 2 was used, and a lognormal distribution for $h(e, a; \gamma, \delta)$, which is assumed to be statistically independent of α with

$$GM = \exp\{-0.05255\, f(e) - 1.626\, g(a)\},$$

$$GSD = \exp\{[0.0003261 \times f(e)^2 - 0.007297 \times f(e) \times g(a) + 0.5648 \times g(a)^2]^{1/2}\}.$$

For lung cancer and female cancers other than ovary, for which γ and δ were assumed to be zero, the statistical uncertainty distributions of log(ERR/Sv) are completely specified by the likelihood profile distributions for $\log(\alpha)$, as shown in Table IV.D.3.

For $e < 30$ and/or $a < 50$, some bias is associated with the assumption of statistical independence

between the linear dose response parameter estimate α and the age-modifier parameter estimates γ and δ, provided the latter two parameters are not assumed to be zero. This bias is a function of e and a, and of the correlations between $\log(\alpha)$ and γ and between $\log(\alpha)$ and δ. As discussed in detail in Appendix C, approach 2 usually overestimates the upper 99% uncertainty for AS, sometimes by as much as 6% (e.g., estimating an upper limit of 53% instead of 50%) for some of the sites in Table IV.D.2 for which the correlation between $\log(\alpha)$ and γ approaches 0.25. For male colon cancer and male urinary organs other than bladder (for which the correlation between $\log(\alpha)$ and δ is between -0.06 and -0.08), and then only for e around 30 and a around 40, the upper limit may be underestimated by as much as 1% (e.g., as 49.5% instead of 50%).

Lymphoma and multiple myeloma, combined into a single group because of small numbers for multiple myeloma, were also evaluated in the manner indicated above, although these cancers were not included in the all solid cancer group used to estimate the common modifying effects. For this category, the ERR for males was positive, while that for females was negative. For the model here, it was assumed that the ERRs for the two sexes were the same although there was a suggestion that they differed ($p = .09$). The common age parameters were used since there was little evidence of departure from these values.

As discussed above, a separate risk estimate was not computed for bone cancer because there were too few cases in the RERF data set. The working group suggests using the residual category estimate for this site.

2. Leukemia.

Site-specific baseline incidence was modeled as a function of gender, city of exposure (Hiroshima or Nagasaki), year of birth, calendar time (where indicated), and age at observation for risk (attained age), as discussed in Preston et al (1994). Default dose-response models were linear (proportional to dose equivalent D in Sv, henceforth called "dose" for brevity) for leukemia associated with exposure to high-LET radiation or low-LET radiation delivered at low dose rates (chronic exposure), and linear-quadratic for leukemia associated with acute exposure to low-LET radiation. The quadratic model was set to have equal contributions of the dose and dose-squared terms at 1 Sv (proportional to $D+D^2$). Fitting a general linear-quadratic (proportional to $D+\zeta D^2$) for all types of leukemia except chronic lymphocytic (CLL) considered as a group, and for acute myelogenous, acute lymphocytic, and chronic myelocytic leukemia separately, various estimates of the unknown parameter ζ were obtained, depending on the type of leukemia, that were greater than zero. However, since all these estimates were statistically consistent with the default value $\zeta=1$, the final models for leukemia and its subtypes were based on $\zeta=1$.

In terms of potential modifying factors such as sex (s), age at exposure (e), attained age (a), and time since exposure (t), the fitted model was

$$\mathrm{ERR}(D,e,a) = (D+D^2)\exp[\log(\alpha) + \beta I_{sex}(s) + \gamma e + \varepsilon t), \qquad \text{(IV.D.4)}$$

where α, γ, and ε are unknown parameters. Parameter α was estimated from the data, as were parameters γ, and ε unless they made no significant contribution to improvement of the fit of the model to the data, in which case they were set to zero. (Following Preston (1994), the leukemia dose response was modeled terms of e and $t = a - e$ instead of e and a.)

Unlike the approach for solid cancers, likelihood profiles for $\log(\mathrm{ERR}_{1Sv})$ were computed for different combinations of sex, exposure age, attained age, and/or time following exposure, as follows: The parameter α corresponds to the excess relative risk when $D+D^2 = 1$, $e=0$ and $t=0$. Thus (for example) the estimated ERR at 1 Sv (ERR_{1Sv}) for leukemia (all types except CLL) among females exposed at age 20 and observed 27 years following exposure can be obtained by replacing e by $e^* = e - 20$ and t by $t^* = t - 27$. The statistical uncertainty distribution of the resulting estimate is described by the profile likelihood distribution of the fitted parameter α. (Tables IV.D.4-IV.D.7). In practice, profile likelihood distributions were computed for formulations of e^* and/or t^* corresponding to various ages and times, and obtained by interpolation for intermediate values.

For leukemia of all types (Table IV.D.4), ERR_{1Sv} was modeled as a function of e and t, but not sex; for acute lymphocytic leukemia (ALL; Table IV.D.5), ERR_{1Sv} was modeled by t for $e < 20$ but for all ages combined for $e \geq 20$, as in Preston (1994); for acute myelogenous leukemia (AML; Table IV.D.6) and chronic myelogenous leukemia (CML; Table IV.D.7), modeling was by time since exposure and, for CML, sex.

3. Thyroid cancer.

Thyroid cancer risk, estimated from the combined analysis data used by Ron et al (1995), required special handling because the data were from 6 different study populations (treating Hiroshima and Nagasaki survivors separately) with possibly different baseline and excess risks. There was no statistically significant dependence of ERR on gender or attained age, and the common attained age parameter value used for most solid cancers was statistically inconsistent with these data; therefore parameters β and δ were both set equal to zero. The final model was

$$\mathrm{ERR}(D,e) = D\exp(\theta_1 I_1 + \ldots + \theta_6 I_6 + \gamma e),$$

where $I_1, \ldots, I_6$ are indicator functions for the 6 study populations and where $\theta_1, \ldots, \theta_6$ are assumed to be normally distributed random variables with common mean θ. Parameter estimates $\boldsymbol{\theta_1, \ldots, \theta_6}$ and γ, and their estimated asymptotic covariance matrix, were obtained by Poisson regression (Hirosoft). The parameter estimate $\boldsymbol{\theta}$ was calculated as the mean of $\boldsymbol{\theta_1, \ldots, \theta_6}$, weighted by the inverse of their estimated covariance matrix $\boldsymbol{\Sigma}$. The off-diagonal elements of $\boldsymbol{\Sigma}$ were positive, indicating that $\boldsymbol{\theta_1, \ldots, \theta_6}$ were positively correlated.

The variance of the estimate θ was adjusted for nonhomogeneity of study populations by the method of DerSimonian and Laird (1986) for meta-analysis of clinical trials, as adapted by Ron et al (1995). The method assumes statistical independence among estimates obtained from different studies, a condition that was not strictly met in the present analysis because a common age-at-exposure parameter was used for the several studies. Since individual study estimates were positively correlated, use of the method is likely to have overestimated the variance of θ and thus resulted in overestimates of the upper uncertainty limits for ERR_{1Sv}.

The statistical uncertainty distribution for θ was assumed to be normal with mean and variance equal to θ and its estimated (adjusted) variance, respectively. $Log(ERR_{1Sv})$ for any given exposure age e_0 was estimated as θ, calculated with e defined as exposure age - e_0 (so that $e = 0$ for exposure age e_0) and was assumed to have a normal uncertainty distribution with GM and GSD as shown in Table IV.D.8 for e_0 in increments of 5. The logarithm of GM is linear in e_0, whereas log(GSD) is markedly curvilinear in e_0 for $e_0 < 20$.

Thyroid is the only cancer site in this report for which the dose-response data were primarily from populations exposed to medical x ray.

4. Skin cancer.

The working group was reluctant to include skin cancers in the present report, because of a high level of uncertainty about how to transfer estimates of ERR/Sv between the Japanese A-bomb survivors and populations in the United States. Non-melanoma skin cancer is not a reportable disease in the United States (although it is in Japan), and baseline rates are not readily available, e.g., from NCI's SEER program (SEER, 1997). However, the NRC review committee report (NRC, 2000) pointed out that estimated rates were available for white and African-American US residents (Scotto, 1983), and recommended that the working group seriously consider including skin among the cancer sites covered by the present report. Also, both DVA and NIOSH expressed interest in having skin cancer estimates.

Our data source was the data set of Ron et al (2000), located at the RERF in Hiroshima. Dale Preston, RERF Chief of Statistics, kindly offered to run analyses for the working group. We initially asked for analyses similar to those for other solid tumors, i.e., using the general model used in Thompson et al, and the model specified in (IV.D.1) and (IV.D.2) of the present report.

For basal cell skin carcinoma, the only subtype for which a significant dose response was obtained by Ron et al (2000), there was a steep decline in ERR/Sv by exposure age, which extended beyond age 30 and was otherwise different from the common trend assumed for other sites, and there was no dependence on attained age. We therefore replaced the age function $f(e)$ specified in (IV.D.2) by

$$f(e) = \min(\max(-30, e-40), 0),$$

(i.e., $f(e) = -30$ for $e \leq 10$, $= e-40$ for $10 < e < 40$, and $= 0$ for $e \geq 40$).

Thus, there was no dependence upon attained age, and constant ERR/Sv, at different levels, for exposure ages less than 10 and 40 or older, with a linear transition in the logarithmic scale between $e = 10$ and $e = 40$. Likelihood profile distributions for ERR/Sv were computed for $e = 10$, 20, 30, and 40, and interpolated for e between 10 and 40 (Table IV.D.9)

For non-melanoma skin cancers other than basal cell carcinoma, which is dominated by squamous cell carcinoma, the unmodified point estimate of ERR/Sv was negative and no convergent estimate could be obtained if an age-dependent modifying term was introduced with either a free or fixed parameter value. We therefore requested a single profile for ERR/Sv, with no modification by age (Table IV.D.9).

The Ron et al data set had only 10 cases of malignant melanoma, far below our inclusion criterion of 50 cases at doses greater than 5 mSv, and we therefore did not include that cancer type.

5. Radon-related lung cancer.

As mentioned above at the end of section IV.C, a 1996 report prepared for the Department of Justice (DOJ, 1996) contains tables of cumulative radon exposures, in working level months (wlm), consistent with point estimates and upper 80% and 90% confidence limits for probability of causation greater than or equal to 50%, and the original data set used for these calculations, but restricted to exposures ≤ 3200 wlm, was made available to the working group. The working group attempted to approximate Appendix Table 3a of the DOJ report, modeling ERR as follows:

$$\mathrm{ERR}(wlm,e,t) = \alpha\, wlm^{\beta} \exp\{\gamma f(a) + \delta g(t)\},$$

where *wlm* is cumulative radon exposure in working level months, a is age at diagnosis, t is time since last exposure, α, β, γ, and δ are unknown parameters, and

$$f(a) = \min[\max(a-45, 0), 30],$$

$$g(t) = \min[\max(t-5, 0), 20];$$

(i.e., $f(a) = 0$ for $a \leq 45$, $= a - 45$ for $45 < a \leq 75$, and $= 30$ for $a > 75$;

$g(t) = 0$ for $t \leq 5$, $= t - 5$ for $5 < t \leq 30$, and $= 20$ for $t > 25$).

Thus, ERR was assumed to be proportional to an unknown power of cumulative exposure in wlm, and to be constant in a (at different levels) for $a \leq 45$ and $a > 75$, and to be constant in t (again, at different levels) for $t \leq 5$ and $t > 25$. Likelihood functions for $\mathrm{ERR}_{1\,wlm}$ are given in Table IV.D.10 or smokers and non-smokers, for $a \leq 45$, $a = 69$, and $a > 75$, and for $t \leq 5$, $t = 15$, and $t > 25$, for interpolation in a and t. For ERR at arbitrary *wlm*, IREP multiplies $\mathrm{ERR}_{1\,wlm}$ by $wlm^{0.82}$.

E. Correction for random and systematic errors in A-bomb survivor dosimetry

Our treatment of random and systematic errors in A-bomb survivor dosimetry was based mainly on the treatment described in Chapter 3 of NCRP Report 126 (1997), and the reader is referred to this material for details. The NCRP approach was also used by the EPA (1999). Dosimetry for the A-bomb survivors is currently being re-evaluated (NAS/NRC, 2001). Revisions in dosimetry could change the estimated risk from gamma rays slightly and might also affect the shape of the dose-response function (Kellerer and Nekolla 1997; Pierce and Preston 2000). In the next year or two, it is expected that revised dose estimates will become available, that uncertainties in these estimates will be evaluated, and that analyses based on the revised doses will be conducted. Uncertainties resulting from systematic biases in A-bomb survivors will need to be reevaluated when these revisions become available. For now, the evaluation from NCRP 26 is used, and the uncertainties discussed below in 2), 3) and 4) should be considered as "place-holders" for a more appropriate evaluation. Changes in dosimetry should not greatly affect the random errors discussed in 1).

For each source of uncertainty, a bias factor with an uncertainty distribution was specified, and this factor was used to correct ERR estimates based on the A-bomb survivor data. Sources of bias and uncertainty that were evaluated by the NCRP are as follows:

1) Uncertainty in the magnitude of random errors in the doses of individual survivors, called R_E in NCRP Report 126, contributed differently to biased uncertainty for solid cancers and the leukemia, for which the forms of the dose response were linear and linear-quadratic, respectively. Unlike the NCRP report, the present report is concerned with individual cancer sites and must consider the two cases separately: uncertain bias correction factors $1+F_L(R_E)$ and $1+F_Q(R_E)$ for cancers with linear and linear-quadratic dose responses, respectively. Pierce et al (1990) recommended a lognormally-distributed random error in individual dose estimates with geometric mean (GM) = 1 and geometric standard deviation (GSD) = exp(0.35), corresponding to an upward correction in estimated risk of 9.0% for solid cancers and 5.6% for leukemia, with essentially no effect on the variability of the corrected risk estimates. There is, however, some uncertainty corresponding to the assumed GSD of the lognormally-distributed random error in dose estimates: the corresponding upward corrections are 6.8% and 4.3% for solid cancers and leukemia, respectively assuming log GSD = 0.30, and 11.4% and 7.2% assuming log GSD = 0.40. If we consider 0.30 and 0.40 to correspond to the 10th and 90th percentiles of an uncertainty distribution for log GSD, and consider that random error in dose assignment can only bias estimated risk downward, it seems appropriate to assume that $F_L(R_E)$ and $F_Q(R_E)$ are lognormal with GM=8.8% and 5.56%, respectively, with common GSD=1.22 (i.e., LN(8.8%, 1.22)) and LN(5.56%, 1.22)).

2) Uncertainty in the appropriate choice of neutron RBE in analyzing A-bomb survivor data,

denoted N_R in NCRP 126 with error factor $f(N_R)$ distributed according to a triangular distribution with minimum 0.9, most likely value 1.0, and maximum 1.1 (i.e., triangular(0.9, 1.0, 1.1)).

3) Uncertainty due to systematic bias in gamma dose estimates, denoted D_γ in NCRP 126 with error factor $f(D_\gamma)$ distributed as triangular(1.0, 1.1, 1.4).

4) Uncertainty due to systematic bias in neutron dose estimates in Hiroshima, denoted D_n in NCRP 126 with error factor $f(D_n)$ distributed as triangular(1.0, 1.1, 1.3).

The overall error factors for random and systematic errors in dosimetry are

$$F_L(D) = (1+F_L(R_E))/(F(N_R)\times F(D_\gamma)\times F(D_n))$$

for solid tumors and

$$F_Q(D) = (1+F_Q(R_E))/(F(N_R)\times F(D_\gamma)\times F(D_n))$$

for leukemia. The uncertainty distributions for $F_L(D)$ and $F_Q(D)$, expressed in percent, correspond reasonably well to normal distributions: N(83.2, 8.36) and N(80.7, 8.05), respectively.

F. Dependence of risk on dose and dose rate for low-LET radiation

Radiations of different quality differ with respect to the shape of the dose-response function for cancer risk. Risk per unit dose of radiations of high linear energy transfer (LET), such as neutrons, alpha particles, or heavy ions, tend to be the same (or greater) at low compared to high doses, whereas for low-LET radiations, such as gamma rays, electrons, x rays, or beta particles, risk per unit dose is thought to be lower at low dose levels. Evidence for a lower risk per unit dose or unit equivalent dose (henceforth to be referred to simply as "dose") of low-LET radiation at low (compared to high) dose levels comes mainly from experimental radiobiology, much of it involving outcomes other than carcinogenesis (NCRP, 1980). Inferences about the shape of the dose-response relationship based on epidemiological studies of cancer, on the other hand, tend to be determined by data in the middle and high dose ranges, i.e., 0.1-1.0 Gy and 1.0 Gy and higher. For solid cancers, generally, there is little persuasive epidemiological evidence of nonlinearity of dose response, whereas for leukemia there is good evidence of positive curvature. The linear-quadratic dose-response model for leukemia used here corresponds to a risk at 0.01 Gy (1 cGy) that is only 0.5% as high as the risk at 1 Gy, or half as high per unit dose.

Linear-model risk coefficients may be reduced by a dose and dose-rate effectiveness factor (DDREF) for estimating risks at low doses and low dose rates. The International Commission on Radiological Protection (ICRP, 1991) recommended a DDREF of 2 for purposes of radiation protection, a value roughly consistent with the default linear-quadratic dose-response model used here for leukemia. The ICRP recommendation is also accepted by the NCRP (1993). In their most recent discussion of the application of DDREF, the United Nations Subcommittee on Effects

of Atomic Radiation (UNSCEAR, 1993) recommended that the chosen DDREF be applied to chronic exposures (dose rates less than 6 mGy per hour averaged over the first few hours) and to acute (high dose rate) exposures at total doses less than 0.2 Gy, a recommendation that was subsequently adopted by the EPA (1999). However, such an abrupt transition seems unrealistic in view of observed linearity of dose response for cancer incidence and mortality among acutely exposed A-bomb survivors, down to and including values below 0.2 Gy (Thompson et al., 1994, Pierce et al., 1996). Also, continuous uncertainty distributions for DDREF have been used by NCRP (1997), EPA (1999), and in a report prepared for the Colorado Department of Public Health and Environment (Grogan et al, 2000) for calculations of lifetime risk of all cancer types combined (Figure IV.F.1). The Grogan et al uncertainty distribution differs from the NCRP distribution mainly in allowing a small probability that risk per unit dose might increase at very low doses. Thus, the NCRP and EPA distributions allowed for the possibility of DDREF values between 1 and 5, while the Grogan et al distribution included values as low at 0.2.

In the present report, ERR is estimated as a function of radiation dose, and modified according to exposure rate (acute or chronic) by application of an uncertain DDREF. The DDREF is applied to all chronic exposures whereas, for acute exposure, the DDREF is phased in as dose is decreased, beginning at an uncertain reference dose less than 0.2 Sv and decreasing smoothly to the value appropriate for chronic exposure. Fractionated acute exposures separated by 5 hours or more are treated as separate exposures; thus, the DDREF is applied to each fraction and their estimated effects on risk are added together. The working group has chosen to derive its own subjective uncertainty distribution for DDREF ($DDREF_{chronic}$) (Figure IV.F.2, left-hand panel), mainly because the analysis of low-dose LSS cancer mortality data (Pierce et al, 1996) is strongly consistent with linearity and suggests, however weakly, the possibility of supra linearity of dose response below 0.5 Sv. A discrete, rather than continuous, distribution was used (emphasizing the subjective nature of the exercise), with nonzero probabilities on DDREF = 0.5, 0.7, 1, 1.5, 2, 3, and 5. For cancers of the female breast and the thyroid gland, a discrete distribution was selected with greater probability at DDREF = 1 (Figure IV.F.2, right-hand panel).

For an *acute* exposure, the DDREF ($DDREF_{acute}$) is modeled as a random quantity that approaches $DDREF_{chronic}$ as dose decreases to zero. Between zero and an uncertain reference dose, D_L (between 0.03 and 0.2 Gy), $DDREF_{acute}$ increases smoothly from $DDREF_{chronic}$ at zero dose to 1 at D_L and above, according to a logistic function of dose (Figure IV.F.3). The uncertainty in the reference dose D_L is expressed as a log-uniform distribution (Figure IV.F.4).

G. Transfer of ERR from the Japanese to the U.S. population

A major concern in using data from Japanese A-bomb survivors to estimate risks for specific cancers in a U.S. population is that baseline risks differ between the two populations and the dependence of radiation risks on baseline risks is not known with certainty. For example, baseline

cancer rates for breast, lung and colon cancer are smaller in Japan than in the United States, while rates for stomach and liver cancer are much higher in Japan. Estimation of risk for a U.S. population based on the dose response coefficients derived from A-bomb survivor data is commonly referred to as the "transfer" or "transportation" problem. A more detailed discussion of the transfer problem appears in NCRP Report 126 (NCRP, 1997).

Two simple solutions are the so-called "multiplicative" and "additive" transfer models, in which estimates of excess relative risk (the ratio between excess and baseline risk) and absolute risk (the difference between the estimated cancer rates with and without exposure), respectively, are applied to the second population (in this case, the U.S. population). The multiplicative transfer model is biologically plausible to the extent that ionizing radiation exposure can be assumed to act as an "initiator" of a process whose likelihood of resulting in cancer depends upon the action of "promoting" agents, if these "promoting" agents are responsible for the difference in baseline rates between the two populations, or, alternatively, if radiation were to act as a promoter of the carcinogenic effects of other agents that are differentially effective in the two populations. In this view, the excess risk from radiation exposure would be greater in a normally high-risk population than in a normally low-risk population. The additive transfer model is plausible to the extent that radiation can be assumed to act mainly as an initiator and the difference between population baseline rates can be assumed to be due to the differential effects in the two populations of other "initiator" carcinogens that act similarly to radiation. In this view, the additional cancer risk burden of radiation exposure would be independent of the population baseline rate.

Several approaches have been used for transferring risk estimates based on the Japanese A-bomb survivor data to other populations. The multiplicative transfer model was used by UNSCEAR (1988) for the world population and in the BEIR V report (NAS, 1990) for the U.S. population. The additive transfer model was used in the BEIR III report (NAS, 1980) and the 1985 NIH report (NIH, 1985). The two transfer models can lead to very different estimates of radiation-related risk for certain cancers for which baseline risks differ greatly between Japan and the U.S. (Land, 1990). Each model receives some support from site-specific comparisons, but there are few sites for which meaningful analytic comparisons can be made. If population differences in cancer rates may be due to both initiating and promoting agents, it is likely that both additive and multiplicative model interactions with radiation may take place, and that some kind of mixture model may be appropriate. For example, the ICRP (1991) used the arithmetic mean of the ERR values obtained by the two transfer models for all solid cancer types combined (Land and Sinclair, 1991), and the Environmental Protection Agency (Puskin and Nelson, 1995) used the geometric mean (except for liver cancer associated with exposure to the radioactive contrast medium thorotrast and bone cancer from exposure to injected ^{224}Ra, for which an additive transfer model was chosen). More recent reports have used uncertain (i.e., randomized) linear or geometric combinations, weighted in various ways, of the additive and multiplicative transfer models for the

estimation of total risk of cancer mortality (EPA, 1999).

Mortality rates for all types of cancer combined vary relatively little by nation, compared to site-specific variation. The initial ERR_{1Sv} value for mortality from all cancers combined used in NCRP Report 126 (NCRP, 1997) was the rounded average of multiplicative and additive transfer model estimates from the LSS mortality data for five different national populations (ICRP, 1991, Land and Sinclair, 1991). Thus, the problem for that report was not how to estimate ERR_{1Sv} for a US population, but to determine the uncertainty associated with estimating ERR_{1Sv} in a particular way. Their solution was an uncertainty factor $f(T)$, distributed as LN(1, 1.3).

For the present report, the problem is how to estimate site-specific and age-specific values of ERR_{1Sv} for the US population in the presence of possibly large differences in baseline rates and the absence of useful information about which model might be correct. Our approach is to use a random linear combination between the additive and multiplicative models,

$$(ERR_{1Sv})_{US} = y \times (ERR_{1Sv})_{mult} + (1-y) \times (ERR_{1Sv})_{add},$$

where the random variable y varies between -0.1 and 1.1. Here, $(ERR_{1\,Sv})_{mult}$ is the site-, sex-, and age-specific excess relative risk at 1 Sv obtained from statistical analysis of the Japanese A-Bomb survivor data and adjusted for random and systematic errors in dose to individual A-bomb survivors (see IV.D above). $(ERR_{1\,Sv})_{add}$ is the same value, adjusted for the corresponding ratio between baseline rates in the two countries:

$$\left(ERR_{1Sv}\right)_{add} = \left(ERR_{1Sv}\right)_{mult} \cdot \left(\frac{B_{Japan}}{B_{US}}\right)$$

Here, B_{Japan} and B_{US} are the sex- and site-specific, age-adjusted background cancer incidence rates in Japan (a surrogate for the A-Bomb survivor cohort) and the US population, respectively, both age-standardized to the world population age distribution (Parkin, 1997).

The coefficient y of the linear combination can be used to favor one model or the other according to the weight of evidence. For instance, y=0 corresponds to the *additive* model, $y = 1$ to the multiplicative model, and $y = ½$ to the arithmetic average of the two. A Monte Carlo simulation is used to express uncertainty about y, with y values sampled according to the following probability density distribution:

$$f(y) = 0.9091 \times \begin{cases} (y+0.1) & -0.1 < y < 0 \\ 1 & 0 \le y \le 1 \\ (1.1-y) & 1.0 < y < 1.1 \end{cases}$$

The constant probability density shown above for y values between 0 and 1 reflects a complete lack of knowledge about the appropriateness of particular weighted averages of the additive and multiplicative transfer models, and the assignment of a small probability weight (9%) to values less than zero and larger than one allows for the (subjectively unlikely) possibility that radiation-related cancer risk might be negatively correlated with population baseline risk. For breast and stomach cancer, more information is available and, thus, the "uninformed" trapezoidal density given above and in Figure V.G.1 may be modified by redistributing some of the weight to the additive transfer model in the case of breast cancer (Land et al, 1980, Little and Boice, 1999, Mattson, 1999) or the multiplicative model for stomach cancer (Griem et al, 1994, Carr et al, 2002). Thus, for breast cancer, a probability weight of 50% was assigned to the *additive* transfer model ($y = 0$), and 50% was assigned to the trapezoidal probability density distribution. For stomach cancer, a probability weight of 33% was assigned to the *multiplicative* model ($y = 1$), and 66% to the trapezoidal distribution, while for thyroid cancer the weighting was 50% on the multiplicative model and 50% on the trapezoidal distribution, reflecting the international basis of the Ron study (1995). The cumulative distribution functions for these distributions are compared with that for the "uninformed" distribution in Figure IV.G.2.

H. Radiation effectiveness factors for different radiation types

People can be exposed to many different types of ionizing radiation including photons, electrons, alpha particles, and neutrons, and the energies of each radiation type can vary widely. Many studies of the effects of ionizing radiation on a wide variety of biological systems, ranging from simple cells to complex whole organisms, have shown that different types of radiation often differ substantially in their biological effectiveness. That is, the probability that a particular biological response is induced by radiation depends on the radiation type and sometimes its energy, as well as the dose. In estimating cancer risks and probability of causation (assigned share) for an individual who received known exposures to particular radiation types, it therefore is essential that differences in the biological effectiveness of the different radiations be taken into account.

Differences in biological effectiveness of different radiation types have long been taken into account in radiation protection. The quantity currently used in radiation protection to describe the biological effectiveness of different radiation types is the radiation weighting factor. This factor is used to modify the dose in an organ or tissue of humans from a given radiation type (the total energy imparted in the organ or tissue divided by its mass), given in Gy, to yield an estimate of equivalent dose, given in Sv. The risk of cancer (or other stochastic radiation effect) in an irradiated organ or tissue is assumed to be proportional to the equivalent dose, independent of radiation type.

The assigned point values of radiation weighting factors used in radiation protection are based on data on the relative biological effectiveness (RBE) of radiations obtained from radiobiological studies of a variety of responses in different biological systems, as well as judgments about the

applicability of estimated RBEs to induction of cancers in humans and theoretical considerations of the relationship between biological effectiveness and the density of ionization produced by different radiations in tissue. The radiation weighting factors currently used in radiation protection include: 1 for photons and electrons of any energy; 20 for alpha particles; and 20 for neutrons of energy 0.1-2 MeV including fission neutrons, 10 for neutrons of energy 10-100 keV or 2-20 MeV, and 5 for neutrons of energy less than 10 keV or greater than 20 MeV. Thus, photons and electrons have a biological effectiveness of 1, by definition, and the radiation weighting factors for the other radiation types represent judgments about their biological effectiveness in humans relative to photons and electrons.

For the purpose of estimating cancer risks and assigned shares in identifiable individuals who received known (estimated) radiation exposures, the term "radiation effectiveness factor," denoted by REF, has been developed to describe the biological effectiveness of different radiation types (Kocher et al., 2002). There are two reasons why a new term, other than "RBE" or "radiation weighting factor," is used. First, "RBE" is not appropriate because this quantity strictly applies only to results obtained from specific radiobiological studies and, thus, should not be used to describe an extrapolation of such results to a different biological endpoint, biological system, or condition of exposure. Second, as discussed above, the radiation weighting factor is a prescribed point quantity, without uncertainty, which is used in radiation protection to calculate equivalent doses, but it is not intended to be used to estimate cancer risks and assigned shares in identifiable individuals who received known exposures. Furthermore, cancer risks and assigned shares are estimated based on estimates of dose without the need to estimate equivalent doses, and it is essential that uncertainties in the biological effectiveness of different radiation types relative to a defined reference radiation be taken into account.

The radiation effectiveness factor for a particular radiation type is used in estimating cancer risks and assigned shares from actual exposures in accordance with one of the following equations:

Solid tumors –

$$\mathfrak{R} = \mathrm{REF_L} \times \frac{R_{\gamma,\mathrm{H}}}{\mathrm{DDREF}_\gamma} \times D \,, \qquad \text{(IV.H.1)}$$

$$\mathfrak{R} = \mathrm{REF_H} \times R_{\gamma,\mathrm{H}} \times D \,, \qquad \text{(IV.H.2)}$$

Leukemias –

$$\mathfrak{R} = a \times \mathrm{REF_L} \times D \,, \qquad \text{(IV.H.3)}$$

$$\mathfrak{R} = a(\mathrm{REF_L} \times D) + b(\mathrm{REF_L} \times D)^2 \,. \qquad \text{(IV.H.4)}$$

In these equations –

- $\mathfrak{R}$ is the risk of a particular cancer (i.e., the excess relative risk, ERR) due to

exposure to a particular radiation type;

- REF is the radiation effectiveness factor for the radiation type and cancer type of concern;
- the subscripts "L" and "H" denote low doses and dose rates and high doses and dose rates, respectively;
- $R_{\gamma,H}$ is the risk coefficient (ERR per Gy) at high doses and high dose rates of the reference high-energy gamma (γ) radiation with a defined biological effectiveness of 1, assuming linearity in the dose-response relationships for all solid tumors;
- DDREF is the dose and dose-rate effectiveness factor, which takes into account that the ERR per Gy for solid tumors at low doses and dose rates of photons (and electrons) may be less than the values of $R_{\gamma,H}$ obtained from studies of exposed populations;
- a and b are the coefficients of the linear and quadratic terms in a linear-quadratic dose-response relationship which is assumed for leukemias under conditions of acute exposure to high-energy gamma rays; and
- D is the estimated dose from the radiation type of concern.

For most solid tumors, the risk coefficients at high doses and dose rates of high-energy gamma rays, $R_{\gamma,H}$, are obtained from studies of the Japanese atomic-bomb survivors. The coefficients a and b in the linear-quadratic dose-response relationship for leukemias under conditions of acute exposure to high-energy gamma rays also are obtained from studies of the atomic-bomb survivors. The data on leukemias indicate that the two coefficients are approximately equal numerically, and this assumption is used in this work. In the radiation effectiveness factor (REF) for the radiation type of concern, the subscripts L and H denote that this factor is estimated based on data on RBE at low doses and dose rates or at high doses and dose rates of the reference radiation, respectively.

The equation selected depends on the particular radiation type and cancer of concern. As discussed by Kocher et al. (2002), eq. (1) for solid tumors is used in cases of exposure to photons, electrons, and alpha particles, eq. (2) for solid tumors is used in cases of exposure to neutrons, eq. (3) for leukemias is used in cases of exposure to alpha particles and neutrons and in cases of chronic exposure to photons and electrons, and eq. (4) for leukemias is used in cases of acute exposure to photons and electrons. Not shown in eqs. (1)-(3) is a factor representing an inverse dose-rate effect, which is applied to all exposures to alpha particles and to chronic exposures to neutrons. This factor, which is a multiplier on the right-hand side of these equations, takes into account that the biological effectiveness of high-LET radiations may be higher under conditions of chronic exposure than under conditions of acute exposure. The use of eqs. (1)-(4) is discussed

further later in this section.

As noted previously, uncertainties in radiation effectiveness factors for different radiation types are taken into account in estimating cancer risks and assigned shares. These uncertainties are described by means of subjective probability (uncertainty) distributions. The assumed probability distributions are intended to represent judgments about the current state of knowledge of the effectiveness of the different radiation types, relative to high-energy gamma rays, in inducing cancers in humans; they are not intended to represent statistical distributions of results that would be obtained if radiobiological studies of the effectiveness of the different radiations in inducing cancers in humans were performed. The factors representing an inverse dose-rate effect for alpha particles or neutrons under conditions of chronic exposure also are described by subjective probability distributions.

The probability distributions of the radiation effectiveness factors used in this report were developed by Kocher et al. (2002) of *SENES* Oak Ridge under contract with the National Institute of Occupational Safety and Health (NIOSH), and have taken into account peer reviews of the work by NIOSH consultants. The assumed probability distributions of the radiation effectiveness factors for photons and electrons are summarized in Table IV.H.1, the distributions for alpha particles are summarized in Table IV.H.2, and the distributions for neutrons are summarized in Table IV.H.3. For photons and electrons, the probability distributions of the radiation effectiveness factors are applied to all cancers, whereas separate probability distributions are developed for leukemias (including lymphomas and lymphocytic cancers) in cases of exposure to alpha particles and neutrons. The probability distributions of the correction for an inverse dose-rate effect are included in the tables for alpha particles and neutrons.

The procedure for using eqs. (1)-(4) in estimating cancer risks and assigned shares is as follows. It is assumed that the exposure history of an individual is given in terms of the equivalent dose, in Sv, to the organ or tissue in which a cancer has occurred—i.e., the dose in that organ or tissue modified by a standard radiation weighting factor, denoted by w_R (formerly called the average quality factor, $\overline{Q}$)—and that the equivalent dose is given for each radiation type (photons, electrons, alpha particles, and neutrons) separately. From the given equivalent dose for a particular radiation type in an organ or tissue (T), denoted by H_T, the dose (D) in that organ or tissue, in Gy, is calculated as $D_T = H_T/w_R$. The dose for each radiation type is the quantity that is input to the calculation of cancer risk and assigned share, and each of these doses is modified by the relevant radiation effectiveness factor in accordance with the appropriate equation.

The treatment of the biological effectiveness of the different radiation types of concern, as represented by the probability distributions of the radiation effectiveness factors summarized in Tables IV.H.1-IV.H.3, differs from the 1985 NIH report in two respects. First, with the exceptions of lung cancer among uranium miners exposed to inhaled radon and its short-lived decay products, with exposure expressed in working level months (WLM), and bone cancer

among patients injected with the short-lived alpha emitter ^{224}Ra, the 1985 report considered only radiations for which the biological effectiveness was assumed to be unity (i.e., photons). It was recognized that, at low doses and dose rates, high-energy gamma rays might be less damaging than lower-energy X rays, but the NIH working group did not have sufficient information to make such a distinction. In the present work, the biological effectiveness of all radiation types (photons, electrons, alpha particles, and neutrons) is taken into account for all cancers, with the exception that radon and lung cancer continues to be treated separately based on estimates of exposure in WLM. In particular, a distinction is made between the effectiveness of high-energy gamma rays and lower-energy X rays, as well as low-energy electrons. The second important difference is that uncertainties in the biological effectiveness of all radiation types relative to high-energy gamma rays are now taken into account. Since the 1985 NIH report focused on radiations that were assumed to be equally effective at any energies, there was no need at that time to consider uncertainties in biological effectiveness.

I. Modification by epidemiological risk factors

Site-specific studies of radiation dose and cancer risk, in LSS sample and in other exposed populations continually followed up over time, generally proceed in a series of steps beginning with the evaluation of evidence that a dose-related excess risk actually exists. Usually, the first modifiers of dose response to be considered are gender, age at exposure, age at observation (attained age), and time following exposure, since information about them is usually obtained at the same time as information on radiation exposure and disease occurrence. Modification of dose response by other factors is a more difficult problem, because it usually requires special data-gathering efforts, such as with an embedded case-control study. Informative studies of interaction between radiation dose and epidemiological risk factors have been carried out for reproductive history in the case of breast cancer and for smoking history in the case of lung cancer.

1. General formulation. If radiation dose D and factor *f* are multiplicative in effect, then the excess relative risk associated with exposure D is independent of *f*, i.e., $ERR_{D|f} = ERR_D$. If D and *f* are additive in effect, then the conditional ERR associated with D given exposure *f* is

$$ERR_{D|f} = ERR_D/(1+ERR_f).$$

2. Breast cancer: interaction of radiation and age at first full-term pregnancy. Reproductive history is known to be an important breast cancer risk factor. In particular, early age at first full-term pregnancy has been shown, in virtually every population that has been studied, to be protective. A case-control interview study of female A-bomb survivors examined the interaction of this risk factor with radiation dose (Land et al, 1994), and found that an additive interaction model was rejected, whereas a multiplicative interaction model was consistent with the data. A general risk model,

$$R_{mix}(D,X;\beta,\theta) = (1 + \alpha_E D)(1 + \beta X/\{1 + \alpha_E D\}^{\theta}),$$

was used to distinguish between the multiplicative model (corresponding to $\theta=0$),

$$R_{mult}(D,X;\beta) = (1 + \alpha_E D)(1 + \beta X),$$

and the additive model (corresponding to $\theta=1$),

$$R_{add}(D,X;\beta) = 1 + \alpha_E D + \beta X.$$

Here, D is radiation dose, X is age at first full-term pregnancy, α_E is a parametric function describing radiation dose response as a function of age at exposure E, and β is an unknown parameter corresponding to X. The maximum likelihood estimate of the parameter θ was negative (-0.25) (Land, 1994) and the likelihood distribution placed less than 10% probability on values greater than zero in calculations performed for the present report. Thus, it appears that very little additional uncertainty would be contributed by allowing for deviations from the multiplicative interaction model, for which no adjustment of ERR_{1Sv} is required for age at first full-term pregnancy. This report therefore makes no uncertainty adjustment for this factor.

3. Lung cancer: interaction of radiation dose with smoking history. Interaction analyses of A-bomb survivors (Blot et al, 1983) and uranium miners (NAS, 1988) failed to discriminate between additive and multiplicative interaction models, although the BEIR IV committee concluded that the data were more consistent with a multiplicative interaction (NAS, 1988). More recently, Lubin and Steindorf (1995) modeled joint relative risks for smoking history (ever vs. never) and exposure to inhaled radon decay products among 6 cohorts of U.S. uranium miners for which such information was available. They concluded that, at that level of smoking history detail, the best-fitting interaction model was intermediate between the additive and multiplicative interaction models. The BEIR VI committee (NAS, 1999) applied the Lubin-Steindorf approach using more recent data, and concluded that both the multiplicative and (especially) the additive interaction models were statistically inconsistent with the data.

In the 1985 NIH report, it was assumed that the interaction of smoking and exposure to low-LET radiation was additive with appropriate assigned shares obtained by multiplying the ERRs by the factors indicated in columns 2 and 3 of Table IV.I.1. These factors were calculated as described on pp. 48-51 of the 1985 report and based on lung cancer relative risks by smoking category given by Rogot and Murray (1980) and the distribution of the U.S. population by smoking status in 1964-65 as published by the National Center for Health Statistics (1967). These factors can be updated by using 1993 information on the smoking status distribution provided by the Centers for Disease Control (1995). This distribution differs substantially from that used in the 1985 report as shown in Table IV.I.2. Because the CDC report did not provide data on amount smoked, it was assumed that among current smokers the distribution by amount smoked was the same as that used in the 1985 report (p.50). It was also assumed that the relative risks by smoking category remained appropriate. The revised factors for additive transportation are given in the last two columns of Table IV.I.1. For the purposes of this report, the ERR_{1Sv} for lung cancer is multiplied

by a factor W_S taken to be $x + (1- x)W_S^*$, where S indexes smoking categories, the W_S^* are the factors given in columns 3 and 4 of Table IV.I.1, and x is assumed to follow a triangular distribution (0, 1, 1.1). This uncertainty distribution allows the ERR_{1Sv} for lung cancer to range from that obtained with an additive interaction ($x = 0$) to that obtained with a multiplicative interaction ($x = 1$), with a probability of about .10 for a super-multiplicative interaction ($x > 1$). The median of this distribution is .74, and at this value, $W_S = 1.97$ for male never-smokers, $W_S = 0.87$ for male ever-smokers, $W_S = 1.75$ for female never-smokers, and $W_S = 0.85$ for female ever-smokers. Thus, at the median value, the ERR_{1Sv} for never smokers is a little more than twice that for ever-smokers. A ratio of two was used by the BEIR VI committee, and was obtained from analyses of uranium miner data (NAS, 1999, pg. 154).

4. Basal cell skin carcinoma: interaction between ionizing and ultraviolet radiation. Ron et al (1998) found significantly different ($p<.02$) ERR_{1Sv} values for basal cell skin carcinoma occurring on the face and hands (0.4, 90% CI -0.1-2.1) and on the rest of the body (4.7, 1.2-1.3), suggesting a sub-multiplicative, or possibly even additive, interaction between UV and ionizing radiation. This finding suggests that ERR_{1Sv} in lighter-skinned, and therefore more UV-sensitive, populations could be less than that observed in the LSS population. On the other hand, Shore et al (2002) reported 124 BCSC cases among 1699 white patients treated by X-ray during childhood for scalp ringworm, cf. 21 among 1035 white nonexposed patients. Among African-Americans, however, only 3 BCSC cases were seen among 525 exposed patients vs 0 among 345 non-exposed patients. This result, unlike that of Ron et al, is inconsistent with additive interaction between ionizing radiation and protection from ultraviolet radiation by skin pigmentation or clothing, as risk factors for BCSC. Judging that we do not now have a good basis for evaluating this interaction, the Working Group has chosen to use the "complete ignorance" uncertainty model discussed in section IV.I above for transfer of the A-bomb survivor-based ERR_{1Sv} estimates for BCSC to the U. S. population and to subpopulations with different baseline BCSC rates.

J. Susceptible subgroups.

Genetic susceptibility to radiation carcinogenesis is known to occur in patients with xeroderma pigmentosum or hereditary retinoblastoma, and the possibility of other such associations is of great interest for theories of carcinogenesis. However, most known genetic syndromes predisposing to cancer are rare, and interactions with radiation dose have not been quantified (ICRP, 1998). Such interactions therefore have not been explored in the present report.

K. Additional sources of uncertainty

As mentioned above (section IV.A), AS is not intended to represent the probability that a particular individual's cancer was caused by his or her radiation exposure, but rather, the fraction of cases of a particular kind of cancer, diagnosed at a particular age among a large group of U.S. residents with a similar exposure history, that would not have occurred in the absence of that exposure. Possible modifying effects of age at exposure, gender, age at diagnosis, and time following exposure, plus (for certain sites) smoking history and reproductive history have been

studied and that information has been incorporated into the model. The working group has also introduced crude uncertainty factors for transfer of risk coefficients between populations with different baseline risks.

It is likely that there are other sources of bias and uncertainty influencing radiation-related risk and AS, about which we have no useful information and, thus, no solid grounds for taking action. However, there may be instances where a case can be made for additional uncertainty. Following the recommendation of the NRC review committee (NRC, 2000) that any additional uncertainty adjustment be documented and justified by an authoritative review panel, we have provided the option for such an adjustment in the expectation that it would be used very rarely, if at all.

V. Features of the Approach

A. This is an interim update.

As noted in III A and B, in the last 15 years additional epidemiologic data have become available, and these data have considerable potential for modifying and refining the AS tables now in use. Also, several efforts have been made to summarize data that were not available at the time the NIH report was published, and to develop risk estimates based on these data. However, these efforts have not evaluated data from studies published in very recent years, including particularly the latest updates of the Japanese A-bomb survivor incidence and mortality data. For example, the most recent BEIR assessment was published in 1990 and the most recent ICRP assessment was published in 1991. Thus, much of the available new data has not yet been evaluated by expert committees charged with developing and recommending risk estimates. In addition, new data, including updated follow-up for cancer incidence in the A-bomb survivors, are currently being evaluated at RERF.

In part because of this situation, the BEIR VII - Phase 1 Committee has recommended that a reassessment of the health effects of exposure to low levels of ionizing radiation be conducted, and the BEIR VII - Phase 2 has been formed to undertake this task. It is anticipated that the present report will be revised after the BEIR VII committee recommendations become available, expected in two or three years. Thus, the AS algorithms described here must be regarded as an interim update rather than one based on risk models endorsed by an official national or international committee; therefore, it might differ appreciably from future tables based on the BEIR VII - Phase 2 report. The current update nevertheless provides AS values that are based on more up-to-date data and models than previously, and also makes notable improvements in the treatment of uncertainties.

B. Similarities to the 1985 report

Because this update must be regarded as interim, the time frame and scope for carrying out data analyses and model development were limited. For this reason, we did not begin from scratch to develop new models, but instead used the models used for the 1985 AS tables as a starting point, amending them as needed to reflect the most important changes in risk coefficients and risk modeling approaches. Specifically, the following features of the 1985 tables were retained:

1. Assigned share estimates based primarily on A-bomb survivor data. The AS values in the 1985 report were based primarily on the A-bomb survivor data, although in some cases other data were also used. The AS values in the current report are based almost entirely on A-bomb survivor data and, with the exception of thyroid cancer, did not directly make use of data from studies of persons exposed for medical reasons, or from studies of workers and others exposed at low doses and dose rates. Estimates based on data from low dose studies would be far too imprecise to meet the needs of the AS tables, where estimates for specific cancer, ages at exposure and gender are required. It is noted, however, that considerable uncertainty has been allowed for extrapolation from high doses and dose rates.

2. Cancer sites evaluated include most of those in the 1985 report. Our choice of cancer sites

includes all but one of those in the previous report. The LSS tumor registry data include only 15 bone cancer cases, too few for inclusion as a separate site. Bone cancer associated with injection of ^{224}Ra, which was included in the 1985 report, was not included in the present report because, although an estimate of radiation-related risk is well-supported by epidemiological data from the Spiess series (Nekolla, 2000), compensation claims associated with injection of ^{224}Ra are highly unlikely to be presented to either the DVA or DOL. Moreover, the remarkable distribution of radiation-related risk over time following injection does not appear to be characteristic of exposure to either gamma ray or other isotopes of radium, and the risk estimates would be difficult to extrapolate to those exposures. Several new cancer categories have been added.

3. Treatment of latent period. The time required for radiation exposure to be reflected in terms of excess cancer risk in an exposed population is very difficult to estimate. In the present report, excess relative risk, which itself may depend on attained age and, in the case of leukemia, on time following exposure, is multiplied by an S-shaped function of time after exposure, that increases from zero immediately after exposure to one after a transition period. The rapidity of the increase depends upon cancer site, with an early increase, becoming appreciable 2 years after exposure and reaching full value after 6 years for leukemia, a somewhat slower increase for thyroid cancer beginning after 3 years and ending after 8 years, and, for all other solid tumors, an increase beginning after 3 years and ending after 14 years. This is only slightly different from the approach of the 1985 report.

C. Important changes

1. Estimates were obtained for all cancer sites for which the calculations could be performed, not just those established as "radiation-related." A working assumption was that radiation exposure might be a causal factor for any site or type of cancer, at some exposure level and under some conditions. This assumption obviates the question of whether or not a particular kind of cancer could be caused by radiation; rather, the most pertinent problem is what values of AS are consistent with current scientific information in a particular instance of cancer following a particular exposure. The working group therefore has provided for the calculation of uncertainty distributions for AS, for all cancer types for which there were relevant data available from the sources on which the present report is based.

2. Assigned share estimates were based on incidence instead of mortality data. Although the 1985 NIH report used incidence data from site-specific studies of leukemia and cancers of the thyroid gland, female breast, and salivary gland, it relied mainly on data from the LSS mortality survey. By contrast, the present report bases its estimates and models on data from the LSS Tumor Registry and, in the case of thyroid cancer, from a pooled analysis of data from several studies. The RERF Tumor Registry is now a highly reliable source of cancer incidence information with good coverage of that part (80%) of the surviving LSS sample resident in the environs of Hiroshima and Nagasaki (Mabuchi, 1994); this coverage goes far toward matching the main advantage of the LSS death certificate data, viz., completeness of ascertainment for a general population of both genders and all ages, acutely and simultaneously exposed to a range of whole-body radiation doses and followed uniformly over time. Follow-up for the mortality series and for incident diseases covered by the Leukemia Registry began on October 1, 1950, the entry date

for members of the LSS cohort; for the LSS Tumor Registry, follow-up began on January 1, 1958. The later beginning of the tumor registry is a serious problem only for cancers of short latency, most of which are covered by the Leukemia Registry or by site-specific studies that involved special case-ascertainment efforts for the period 1950-1957, and for estimation of excess risk among persons who were over 50 or 60 years of age when exposed. Comprehensive statistical analyses of site-specific cancer incidence through 1987 were presented for solid cancers and leukemia (Thompson, 1994, Preston, 1994) and, especially important for present purposes, the original data sets were made available by RERF on disk or downloadable from the RERF web site.

3. Assigned share estimates are based on analyses conducted for this specific purpose instead of published risk estimates. For the 1985 report, assigned shares were estimated from tabulated published estimates, primarily from the BEIR III report. The availability of grouped numerator and denominator data from LSS Tumor Registry for 1958-1987, plus similar data from a site-specific incidence study of skin cancer and a pooled study of thyroid cancer in several irradiated populations, allowed the present working group to model site-specific risks directly. This permitted the working group to determine independently the dependence of dose-specific excess relative risk on important modifying factors, and to choose models of suitable complexity.

4. Modeling of the excess relative risk (ERR) instead of the excess absolute risk (EAR). The ERR was modeled directly rather than converted from tabulated estimates of EAR, as was done in the 1985 report. Note that assigned share (AS) is a simple, monotonic function of the ERR, AS = ERR /(1+ERR).

5. More attention to attained age. For all cancer types except leukemia and bone cancer, the 1985 report models were based on the assumption that, after a minimal latent period, the excess relative risk per Sv (ERR/Sv) remained constant over time since exposure and therefore did not depend additionally upon attained age. New information from analyses of A-bomb survivor information suggests that this may not be the case generally. Modeling for the present report allows for the possibility that ERR/Sv may depend upon attained age as well as age at exposure..

6. Different default assumptions for dependence of ERR/Sv on exposure age and attained age. In the 1985 report and in the 1990 draft report presented to the NRC review committee, site-specific estimates of ERR/Sv were fitted separately by site, and were assumed not to depend upon sex, age at exposure, or attained age unless there was site-specific statistical evidence to the contrary. The NRC review subcommittee recommended that consideration be given to conducting joint analyses of several cancer types (see Pierce and Preston, 1993), testing whether various parameters were comparable among cancer types, and then using common estimates of selected parameters in developing site-specific AS values. This approach has the potential advantage of greater statistical precision in the estimated AS values, but the disadvantage of difficult-to-quantify uncertainty in whether the chosen models are appropriate. Our approach was to estimate parameters for modification of ERR/Sv by exposure age and attained age for all solid cancers combined and to use these as default values for site-specific estimates. Thus, values fitted from site-specific data alone were used only if they differed significantly from the default values. Type-specific leukemia estimates were based on type-specific data only, and included nonzero

modifying parameters by time, exposure age, or attained age only if required.

7. Radiation dose response and adjustment for low dose-rate exposure Because estimates obtained directly from epidemiological data on populations exposed only at low doses are very imprecise, it is necessary to extrapolate from risks that have been estimated from persons exposed at higher doses (and dose rates) than those of direct interest. The estimates used in this report are based on Japanese atomic bomb survivor data, and estimates based on these data tend to be driven by the cancer experience of persons exposed to doses that exceed 1 Gy. This is much larger than doses for which AS values are usually desired, which are almost always less than 0.1 Gy and often much smaller.

Although most epidemiological data for solid cancers are compatible with a linear dose-response function in which risk is proportional to dose, curvilinear forms cannot be excluded. On the other hand, dose-response analyses of leukemia risk have consistently shown evidence of upward curvature consistent with a quadratic function of dose having a substantial linear component ("linear-quadratic" or "L-Q" for short).

a. Method used in the 1985 NIH report The 1980 BEIR III committee chose as their "preferred" dose response model an L-Q model in which risk was proportional to $D + D^2/1.16$, where D is organ-specific dose in Gy, and the 1985 NIH tables committee adopted that form for their report. Thus, with two exceptions (breast and thyroid cancer, for which linearity was assumed), the estimated excess risk per unit dose was a little more than half as high at 0.1 Gy as at 1 Gy. Another consequence was that the risk per unit dose of the sum of several exposures, each less than 0.1 Gy and separated in time, or a chronic exposure (treated much the same as the sum of many very small exposures) was estimated to be about half as high as that for a single, acute exposure of about 1.2 Gy.

b. Method used in the present report The approach used for the present report was to treat leukemia risk as proportional to $D + D^2$, since estimates of the D^2 coefficient are generally inexact but in the neighborhood of unity and significantly greater than zero. For all other cancers, the risk was assumed to be linear (proportional to D) for curve-fitting purposes but with a dose-and-dose-rate-effectiveness factor (DDREF) applied to reduce estimated risk at low doses and dose rates. The DDREF approach was chosen because it is consistent with recommendations by the International Commission on Radiation Protection (ICRP, 1991) and because instances of a linear dose response have been observed above a certain level in combination with a DDREF of 2 or more at lower levels, in experimental studies of radiation carcinogenesis using fractionated exposures (R. Ullrich, personal communication).

8. Transfer of estimates between populations. An important source of uncertainty is the applicability of risk estimates derived from Japanese A-bomb survivor data to a contemporary U.S. population, especially for cancer types where baseline risks for the two countries differ markedly. On the basis of comparisons of leukemia and breast cancer risk in different populations (BEIR III, Land et al, 1980), transfer between populations in the 1985 NIH report was based on the assumption that absolute risks were comparable, and no attempt was made to evaluate the uncertainty resulting from this choice. For most cancer sites, however, there are few quantitative

data other than those available from the LSS, and it cannot be excluded that other transfer models may be appropriate for different cancer sites (Land 1990, Land and Sinclair 1993, NCRP-126, EPA 1999). Moreover, the choice of transfer model involves considerable uncertainty. In the current report, uncertainty from this source has been evaluated, with central estimates chosen to fall in between the NIH model and a model in which relative rather than absolute risks are assumed comparable for Japanese and US populations. Cancers of the female breast, thyroid gland, and skin were treated somewhat differently, as discussed in IV.G above.

9. Biological effectiveness of different types of radiation. The 1985 NIH report considered exposure to low-LET radiation (i.e., photons) only, since this was the principal type of radiation to which the Japanese atomic-bomb survivors were exposed. The results of that study thus were not applicable to exposures to high-LET radiation, such as neutrons and alpha particles, which have a greater biological effectiveness per unit dose than low-LET radiation. The 1985 report also did not take into account that low-energy photons and electrons may have a greater biological effectiveness than the high-energy gamma rays to which the atomic-bomb survivors were exposed. In contrast, the present report considers exposures to different radiation types, including photons, electrons, alpha particles, and neutrons. The biological effectiveness of different radiations is represented by the radiation effectiveness factor (REF), which generally depends on the radiation type and its energy. For each radiation type and energy of concern, the REF is described by a probability distribution that is intended to represent uncertainties in relevant data obtained from radiobiological studies.

10. Treatment of uncertainty. The treatment of uncertainty is similar to that in the 1985 report in that uncertainties from each of several components or sources are evaluated separately and then combined into an overall assessment based on the assumption that uncertainties from different sources are independent. It is also similar in that many sources could not be evaluated using rigorous statistical procedures, but required subjective judgements of the investigators. However, the treatment of uncertainties in the updated report differs from the 1985 report in several respects. First, components of uncertainty that were not evaluated earlier have been added, including especially statistical variability in the risk coefficients and uncertainty resulting from transferring risk coefficients based on Japanese A-bomb survivors to a contemporary U.S. population. Second, uncertainty distributions were selected to reflect available data and the best judgment of the investigators, and were not limited to log-normal distributions as was the case in 1985. Third, Monte Carlo simulations were used to combine uncertainties, a feature that made flexible selection of uncertainty distributions possible. Fourth, uncertainty was not treated as an "add-on", developed after the central estimates had been determined, but rather was a fundamental part of the process. That is, emphasis was not on determining single point estimates, but on developing overall uncertainty distributions, calculated by combining the uncertainty distributions from each of the contributing sources. Given an uncertainty distribution, it is of course possible to determine medians, means, and various percentiles or credibility limits. Finally, the on-line computer software (IREP) incorporates "customized" Monte Carlo simulations to obtain the distribution of a desired AS, taking into account the exposure scenario, certain characteristics of the individual, and the specific type of cancer.

The above modifications drew heavily on developments in uncertainty analysis that have occurred since 1985. The BEIR V report used Monte Carlo simulations to evaluate statistical uncertainty in lifetime risks, but relied on lognormal propagation of errors for evaluating several other uncertainty sources. More recently, both NCRP and EPA have used Monte Carlo simulations, including flexible choice of distributions to describe uncertainties from individual sources. However, NCRP and EPA were primarily concerned with uncertainties in lifetime risks to populations rather than uncertainties in risks for individuals with specific characteristics. Furthermore, NCRP provided a distribution only for the lifetime risk of all fatal cancers, although the report contains discussion of specific cancer types. To our knowledge, the work reported here is the first to evaluate uncertainty distributions for specific AS values associated with any of a wide range of specific cancer types, individual characteristics, and exposure scenarios.

VI. Use of the AS estimates and their uncertainties for adjudication.

This report makes no recommendations regarding how the estimated assigned shares and the accompanying software IREP should be used to adjudicate claims. However, some possible applications of the 1985 tables are briefly described below. Further discussion of applications is provided by NAS-NRC (2000).

One approach is to use a sliding scale, and British Nuclear Fuels developed such a compensation scheme based on the 1985 tables (with some modifications) (Thomas et al. 1991; Wakeford, 1999). Under this scheme, persons whose estimated AS values are 50% or higher receive full awards, whereas persons whose estimates are between 20% and 50% receive graduated partial awards. This approach makes no use of uncertainties, but avoids the arbitrariness of a full award for a person with an dose that results in a PC of exactly 50%, and nothing for a person with a slightly lower dose that results in a PC of 49%.

Another approach is an "all or nothing" approach in which a full award is granted if the PC exceeds some specified value, and no award is granted if the PC is less than the specified value. When 50% is the chosen cutoff value, this approach can be considered as based on tort law in which claims are awarded if it is at least as likely as not that the cancer was caused by radiation.

CIRRPC (1988) developed a procedure for screening claims of radiation-induced cancer that made extensive use of uncertainties in the PCs that were provided in the 1985 NIH report. Under this scheme, a person passes the screening if the upper 99% confidence limit (or some other chosen level) on the estimated PC exceeds 50%. The CIRRPC report notes that:

> "This procedure is designed to insure that cases which have even a small chance of a true PC, that is 0.5 (50 percent) or greater (i.e., that meet the "as least as likely as not" criterion), are developed for assessment of causality, yet will avoid detailed development of those cases for which there is virtually no chance that the true PC would be as large as 50 percent. The screening process is not a decision-making process that should result in automatic compensation."

The DVA has subsequently used the screening doses (based on the upper 99% confidence limit) developed by CIRRPC. In practice, few cases who have passed the screening have failed to receive rewards. This policy has the advantage that is highly unlikely to exclude persons with meritorious claims. However, it is likely to award many persons whose true PCs are very much less than 50%, a use of funds that some might question. It also has the anomaly that the more uncertain the PC estimate the more likely that a claimant will be awarded. For example, as noted in the NAS review of this report (2000), a claimant with a precisely estimated PC of 44% (CI: 41%-47%) would fail to receive an award, while a claimant with an imprecisely estimated PC of 9% (CI: 0%-82%) would be awarded..

Both the sliding scale approach and the "all or nothing" approach as practiced by the DVA could be varied in many ways. For example, PCs other than 50% could be used as the basis of awards, and less stringent upper confidence limits (e.g. 90% instead of 99%) could be used. Compensation based on the years of life lost from the cancer has also been proposed and has

certain advantages (Robins and Greenland 1991).

A purely numerical consideration is that estimates obtained by Monte Carlo simulation of the 99th percentile of a probability distribution are unstable unless based on a very large sample size. For example, an estimate based on a simulated sample of size 100 is determined by the two highest values. With a sample of 1000 the estimate depends upon the highest 11 values, and for a sample of 10,000 it depends upon the largest 101 values. The estimate based on 100 simulations is obtained very quickly but is highly unstable, whereas that based on 10,000 simulations is reasonably stable but requires a longer time to calculate.

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APPENDIX A: Text of Congressional Mandate and Excerpt from Presidential Statement

Public Law 97-414 - January 4, 1983

"7(b)(1) Within one year after the date of enactment of this Act, the Secretary of Health and Human Services shall devise and publish radio-epidemiological tables that estimate the likelihood that persons who have or have had any of the radiation-related cancers and who have received specific doses prior to the onset of such disease developed cancer as a result of these doses. These tables shall show a probability of causation of developing each radiation related cancer associated with receipt of doses ranging from 1 millirad to 1,000 rads in terms of sex, age at time of exposure, time from exposure to the onset of the cancer in question, and such other categories as the Secretary, after consulting with appropriate scientific experts, determines to be relevant. Each probability of causation shall be calculated and displayed as a single percentage figure.

(2) At the time the Secretary of Health and Human Services publishes the tables pursuant to paragraph (1), such Secretary shall also publish--

> (A) for the tables of each radiation related cancer, an evaluation which will assess the credibility, validity, and degree of certainty associated with such tables; and
>
> (B) a compilation of the formulas that yielded the probabilities of causation listed in such tables. Such formulas shall be published in such a manner and together with information necessary to determine the probability of causation of any individual who has or has had a radiation related cancer and has received any given dose.

(3) The tables specified in paragraph (1) and the formulas specified in paragraph (2) shall be devised from the best available data that are most applicable to the United States, and shall be devised in accordance with the best available scientific procedures and expertise. The Secretary of Health and Human Services shall update these tables and formulas every four years, or whenever he deems it necessary to insure that they continue to represent the best available scientific data and expertise."

Excerpt from President Reagan's statement on the occasion of his signing the Orphan Drug Act.

> ". . . there is as yet no consensus among radiation experts in relating human cancers and exposure to low levels of radiation. Yet, Section 7 mandates that probability of causation tables be calculated for even very small dose levels. Accordingly, I am directing the Secretary of Health and Human Services to complete the tables to the extent that may be possible and scientifically responsible, in light of the analysis also mandated by Section 7, which requires him to 'assess the credibility, validity, and degree of uncertainty associated with such tables.'"

APPENDIX B: DHHS Charter - Ad Hoc Working Group to Develop Radioepidemiological Tables

"Purpose

Section 7(b) of Public Law 97-414 directs the Secretary of Health and Human Services to devise and publish radioepidemiological tables that estimate the likelihood that persons with any radiation-related cancer who received specific radiation doses before the onset of the cancer developed the disease as a result of such exposure. The tables must show the probability of causation for each cancer associated with receipt of doses ranging from 1 millirad to 1,000 rads in terms of sex, age at time of exposure, time from exposure to disease onset, and such other categories as the Secretary, after consultation with appropriate scientific experts, determines to be relevant. In carrying out this mandate, the Secretary deems it necessary to establish an Ad Hoc Working Group to Develop Radioepidemiological Tables comprised of scientific experts whose qualifications will insure a thorough, competent and timely completion of the task.

"Authority

42 U.S. Code 217a, Section 222 of the Public Health Service Act, as amended.

This Ad Hoc Working Group to Develop Radioepidemiological Tables is governed by the provisions of Public Law 902-463, which sets forth standards for the formation and use of advisory committees.

"Function

In addition to developing radioepidemiological tables, the Ad Hoc Working Group shall:

7. Assess the credibility, validity, and degree of certainty associated with such tables; and

8. Compile the formulas that yielded the probabilities of causation listed in such tables. Such formulas shall be published in such a manner and together with information necessary to determine the probability of causation of any individual who has or has had a radiation-related cancer and has received any given dose.

The tables specified in paragraph (1) and the formulas specified in paragraph (2) shall be devised from the best available data that are most applicable to the United States, and shall be devised in accordance with the best available scientific procedures and expertise. The Secretary of Health and Human Services shall update these tables and formulas every four years, or whenever necessary, to insure that they continue to represent the best available scientific data and expertise.

"Structure

The Ad Hoc Working Group to Develop Radioepidemiological Tables shall consist of eight members, including the chairperson. Members and chair- person shall be selected by the Secretary, or designee, from outstanding authorities in the fields of endocrinology, radiation

biology and pathology, radioepidemiology, biostatistics, and radiobiology. Members shall be invited to serve for a period of one year. Management and support services shall be provided by the Office of the Director, National Institutes of Health.

"Meetings

Approximately eight meetings shall be held at the call of the chairperson who shall also approve the agenda. A government official shall be present at all meetings. Meetings shall be conducted and records of proceedings kept as required by applicable laws and Department regulations. Meetings shall be open to the public, except as determined otherwise by the Secretary; notice of all meetings shall be given to the public.

"Compensation

Members who are not full-time Federal employees shall be paid at the rate of $100 per day, plus per-diem and travel expenses in accordance with Standard Government Travel Regulations.

"Annual Cost Estimate

Estimated annual cost for operating the Ad Hoc Working Group, including compensation and travel expenses for members but excluding staff support, is $36,700. Estimated annual man years of staff support required is one at an estimated annual cost of $49,213.

"Reports

Section 7(b) of Public Law 97-414 directs that within one year after the date of enactment of this Act (January 4, 1983), the Secretary of Health and Human Services shall publish the radioepidemiological tables. The Ad Hoc Working Group will complete its task as outlined in the Function section of this document and submit these findings to the Director, National Institutes of Health, by October 15, 1983.

"Termination Date

Unless renewed by appropriate action prior to its expiration, the Ad Hoc Working Group to Develop Radioepidemiological Tables will terminate on May 15, 1984.

Approved:

8-4-83
Date

(signed) Margaret M. Heckler"
Secretary

APPENDIX C: Bias associated with assuming statistical independence between estimates of dose response and estimates of modifying factors.

The magnitude of the bias can be estimated, for sites computed using approach 1 (Table IV.D.1), as follows: the inverse of the 99% upper statistical uncertainty limit (computed using lognormal assumptions) for ERR at 1 Sv is the dose, in Sv, for which the upper 99% uncertainty limit of AS is 50% (AS = ERR/(1+ERR) = 0.5 if ERR = 1). The corresponding ERR, also computed using lognormal assumptions but with the approach 2 assumption of zero covariance between $\log(\boldsymbol{\alpha})$ and $h(e, a; \gamma, \boldsymbol{\delta})$, is likely to be either higher or lower than 50%, thus indicating the direction and magnitude of bias using the decision rule selected by the DVA, and mandated by the Energy Employees Occupational Illness Compensation Program Act of 2000. The percentages of over- or under-estimation of AS using approach 2, for the five approach 1 sites, are shown in Appendix Table C.1 for exposure ages $e = 18$, 20, 25, and 30 (or over) and attained ages $a = 25$, 30, 35, 40, 45, and 50 (or over), where $a \geq e + 7$.

Approaches 1 and 2 always give the same result for $e \geq 30$ and $a \geq 50$, where ERR is assumed not to depend upon γ and δ; otherwise, Appendix Table C.1 suggests that approach 2 usually overestimates the 99% upper limit for AS when that limit is near 50%, and apparently never underestimates it for stomach cancer among females. The non-trivial exceptions occur for liver cancer, female breast cancer, and digestive cancer among males when $e \geq 30$; they are underestimation by 0.7% to1% (i.e., estimating the 99% upper limit for AS to be as low as 49.5% when it should be 50%) for a around 45, and underestimation by 1.3% to 2% (estimating the limit to be as low as 49% when it should be 50%) for a around 40. The correlation between $\log(\boldsymbol{\alpha})$ and $\boldsymbol{\delta}$ is -0.8 or lower for the three sites with non-trivial underestimation of the 99% upper limit for AS when calculated assuming zero covariance between $\log(\boldsymbol{\alpha})$ and $h(e, a; \gamma, \boldsymbol{\delta})$, and -.01 or higher for the other two. According to Appendix Figure C.1, only for male colon and male urinary cancer, among sites for which approach 2 was used, is the correlation between $\log(\boldsymbol{\alpha})$ and $\boldsymbol{\delta}$ lower than -0.4. This suggests that downward bias of the 99% upper limit for AS by as much as 1% is a potential problem only for these two cancers, and then only for $e \geq 30$ and a around 40.

APPENDIX D: Computational Details

Uncertainty due to sampling variation

As described in Section IV, uncertainty due to statistical variation was approximated by fitted lognormal distributions for 5 site-sex combinations in Table IV.D.1 and for thyroid cancer. For other cancers it was calculated by likelihood profile distributions for the dose-response parameter, either interpolated among different values of exposure age, attained age, and/or time following exposure, or in combination with fitted lognormal uncertainty distributions for age-related modifiers of dose response. These uncertainty models were based on analyses of A-bomb survivor cancer incidence data, and were obtained for the ERR_{1Sv} associated with each type of cancer.

For use in IREP, the likelihood profile distributions were specified in cumulative form by quantiles (0.25%, 0.50%, 1.25%, 2.50%, 5.00%, 12.50%, 15.85%, 50% (approximated by the maximum likelihood estimate), 84.15%, 87.50%, 95.00%, 97.50%, 98.75%, 99.50%, and 99.75%). Intermediate values were calculated by cubic spline interpolation (Press et al., 1996). For all cancer types other than leukemia, 400 interpolated points were used to define the likelihood functions. For leukemia, the $ERR_{1\,Sv}$ depends on both age at exposure and time since exposure (see below). Therefore, only one hundred interpolated points were used, in order to reduce the size of the electronic files.

To obtain the $ERR_{1\,Sv}$ for any age at exposure, age at diagnosis, and/or any time since exposure, linear interpolation in the logarithmic scale was performed between the tabulated $ERR_{1\,Sv}$ values. The $ERR_{1\,Sv}$ for leukemia depends on both the age-at-exposure and time-since-exposure. In this case a bilinear two-dimensional interpolation was performed (Press et al. 1996). From the numerical point of view, the cubic spline interpolation between percentiles was performed first. Then, the log-linear interpolation between ages-at-exposure or times-since-exposure was performed for each derived percentile of the likelihood function.

Phasing in the latency period

The analyses described in Section IV-C were based on a model in which the risk was assumed to be very low (or zero) for a specified minimal latency period after exposure. To avoid an abrupt jump in the ERR, we used a set of scaling factors to estimate the $ERR_{1\,Sv}$ for the years between the end of the latency period and the age at which maximum risk occurs.

For leukemia (all types), the latency period is considered to end 2 years after exposure, although the Life Span Study data cover only the period 5 years and more after exposure. Accordingly, we phased in the fitted ERR, allowing full expression 5 years after exposure. For 2, 3, and 4 years after exposure, the $ERR_{1\,Sv}$ is estimated as 0.25, 0.5, and 0.75, respectively, times the fitted value for $ERR_{1\,Sv}$ at 5 years after exposure.

The minimum latency period for thyroid cancer was assumed to be about 5 years, and there was no statistically significant evidence of a trend in ERR_{1Sv} with time following exposure. For a smooth transition, reduced values of $ERR_{1\,Sv}$ were computed for years 3, 4, 5, 6, and 7 years after exposure by multiplying the fitted $ERR_{1\,Sv}$, specific to each age at exposure, by 0.1, 0.25, 0.5, 0.75, and 0.9, respectively. The risk of thyroid cancer in the first three years (i.e., 0, 1, and 2) after exposure is considered to be zero.

For all other cancers, an S-shaped function similar to the one used to describe the DDREF (see the following section) was used to insure a smooth transition in $ERR_{1\,Sv}$. The mid-point of the S-shaped function (i.e., the time since exposure at which the $ERR_{1\,Sv}$ is half of the maximum $ERR_{1\,Sv}$) is 7.5 years. Given the lack of precise knowledge about the on-set of different cancers, the mid-point was allowed to vary around the central value of 7.5 years after exposure. Thus, the uncertainty in the mid-point was described as a triangular distribution with a minimum of 5, a mode of 7.5 and a maximum of 10 years after the exposure. An S-shaped curve using this uncertain mid point produces a negligible $ERR_{1\,Sv}$ for times after exposure less than 3 years and reaches the maximum $ERR_{1\,Sv}$ at 14 years after exposure.

The dose and dose-rate effectiveness factor (*DDREF*)

As discussed in IV.F, for an *acute* exposure, the value $DDREF_{acute} = 1$ is used for doses larger than a randomly generated reference dose D_L, above which the dose response is assumed to be linear. As the dose approaches zero, $DDREF_{acute}$ approaches the values prescribed for chronic exposure, $DDREF_{chronic}$. The mathematical formulation for the transition from $DDREF_{acute}$ =1 at $D = D_L$ to $DDREF_{acute} = DDREF_{chronic}$ at D = 0, as graphed in IV.F.2, is as follows:

$$DDREF_{acute} = \begin{cases} 1 & \text{if } Dose \geq D_L \\ \left\{ 1 - \left[\dfrac{\left(1 - \dfrac{1}{DDREF_{chronic}}\right)}{1 + e^{\frac{(Dose - 1)}{s}}} \right] \right\}^{-1} & \text{if } Dose < D_L \end{cases}$$

The parameters I and S are, respectively, the inflection point ($I = 0.5 \times D_L$) and the "shape" parameter (S = I/ln(500)); the smaller the values for S, the steeper the increase of the logistic function 1 + exp((Dose - I)/S).

Note that, as the dose approaches zero, the $DDREF_{acute}$ approaches the prescribed $DDREF_{chronic}$. The value of the "shape" parameter was chosen to obtain the least steep increase of the logistic function that still reproduces the $DDREF_{chronic}$ for a zero dose[1].

[1] This relationship ensures that the DDREF for a dose equal to D_L is larger than 0.99.

Appendix E. Comparison of results from IREP with results from the 1985 NIH report and CIRRPC.

As noted in Section VI, the DVA has based its claims procedure on screening doses that were developed by CIRRPC (1988). These doses were based on the upper 99% credibility limits of the uncertainty distributions for the estimated PCs. Although the development of the screening doses was based on the 1985 NIH report, CIRRPC (1988) modified the PCs (to account for bias) and expanded the uncertainty assessment given in the original NIH report. As noted in Section VI, persons who pass the VA screening procedure usually receive an award even though CIRRPC notes that

> Passing the screening criteria should not be equated with having established causality. A claim based on an exposure to radiation that just passes the screening criteria has only a very remote chance of resulting in a meritorious finding after further development of causality.

In this appendix, we compare the median ERRs from IREP with the ERRs from the 1985 NIH report, and also with the ERRs that formed the basis of the CIRRPC recommendations. We also compare the CIRRPC screening doses with those that would be obtained using the upper 99% credibility limit based on models developed in this report.

We note that CIRRPC made use of the uncertainty evaluation from the 1985 NIH publication, but modified it by adding an evaluation of statistical uncertainty, increasing the age at exposure uncertainty, and adding a positive probability of a linear dose-response in the uncertainty evaluation for the DDREF. We note particularly that the change in the DDREF uncertainty evaluation shifted the ERR distributions upward by a factor of about 1.5 for cancers other than breast and thyroid cancer, which were based on linear dose-response models with no uncertainty assumed for the DDREF. In addition, the 1985 NIH report estimated that ERRs based on Japanese atomic bomb survivors were too low by a factor of 1.62 because dosimetry revisions that eventually led to the DS86 dosimetry system had not yet been incorporated. For this reason, CIRRPC increased those ERRs that were based on atomic bomb survivor data by a factor of 1.62.

For the purpose of providing doses for screening claims, CIRRPC made the additional assumption that the claimant had a baseline risk at the 10^{th} percentile of the distribution of the baseline risks for the cancer of interest among all counties of the United States, and the further assumption that the ERR was inversely proportional to the baseline risk For most cancers, these two assumptions led to increasing the ERRs (and decreasing the screening doses) by a factor of 2 or more. For lung cancer, the CIRRPC screening doses for those with unknown smoking status were based on non-smokers, whereas screening doses for those who were thought to be smokers were based on those with unknown smoking status. For leukemia, CIRRPC screening doses for cases occurring less than 20 years after exposure were based on the assumption that the leukemia occurred at the

time yielding the maximum PC or ERR; for cases occurring 20 or more years after exposure, CIRRPC screening doses were based on the assumption that leukemia occurred 15 years after exposure.

Appendix Tables E.1, E.2, E.3 and E.4 are addressed at helping readers compare results based on the model described in this report (and implemented with IREP) with results based on the earlier NIH report and on CIRRPC recommendations. For each of the cancers evaluated by CIRRPC, the first three tables show ERRs for a male exposed to a chronic dose of .01 Sv at age 20 (Appendix Table E.1), age 30 (Appendix Table E.2), or age 40 (Appendix Table E.3) and developing cancer at age 50 or older. Additional scenarios are shown for leukemia. Shown in the tables are the original ERRs from NIH (1985) (column 2), modification factors used by CIRRPC (column 3), the ERRs after adjustment for these factors (column 4 in bold), and the medians of the ERR distribution generated by IREP (column 7 in bold). These three tables also show the deliberately biased CIRRPC ERRs based on the assumption of a low baseline risk (column 6).

Several factors contribute to differences in the ERRs from IREP (column 7) and the CIRRPC ERRs shown in column 4 (bold). The reader should consult Section V.C for a complete discussion of these differences. Most important, the IREP ERRs were based on cancer incidence data for the A-bomb survivors for the period 1958-87, whereas most of the NIH (1985) ERRs were based on mortality data from 1950 through 1974 or 1978. The data used by IREP include about 8600 cancers, more than twice the number evaluated earlier. For thyroid cancer, the data used by IREP were also much more extensive than those considered by NIH (1985).

The ERRs from NIH (1985) were based on age-specific absolute risk estimates, and many of these may have been statistically quite unstable, especially those for less common cancers. For most cancers, the effects of age at exposure are much stronger for NIH (1985) than IREP, and for this reason, results tend to be more comparable for older exposure ages. The NIH (1985) age at exposure effects were obtained by evaluating ratios of age-specific absolute risk estimates and age-specific baseline risks with each cancer site treated separately, whereas IREP age at exposure effects were obtained by estimating a single parameter based on all solid cancers. The longer follow-up period available for developing IREP is particularly important for evaluating the modifying effects of age at exposure, and is especially important for evaluating risks for those who were young at the time of exposure. The longer follow-up period is also important for evaluating the effects of attained age, and another reason for differences in NIH and IREP ERRs is that the latter allowed for attenuation with attained age.

Still another reason for differences is that NIH (1985) was based entirely on additive transfer between populations, whereas IREP uses an uncertain mixture of additive and multiplicative transfer, with the additive proportion uniformly weighted over the interval 0 to 1. This is especially important for cancers of the esophagus, stomach, and liver, where baseline risks are much higher in Japan than in the US population. NIH (1985) also used a strictly additive model

to account for the interaction of smoking and radiation in evaluating lung cancer risks, whereas IREP is based on a model that is intermediate between additive and multiplicative. The IREP approach decreases ERRs for smokers but increases ERRs for non-smokers as compared with the NIH (1985) approach.

Appendix Table E.4 shows the 99% screening doses from CIRRPC Table 3 for persons exposed at ages 20, 30 and 40. As noted in Section VI, the DVA has used these doses as a basis for awarding claims. Also shown (in parentheses) are the 99% screening doses that would have been obtained without the upward adjustment based on the assumption that claimants had a low baseline risk; these doses may be more appropriate for comparing with results obtained from IREP. The table also shows the doses that would yield an upper 99% confidence limit for the PC of 50% based on IREP. Unlike the results in Appendix Tables E.1, E.2, and E.3, the results in Appendix Table E.4 depend on the uncertainties in the estimated ERRs as well as the level of the ERR. The uncertainty evaluation used for IREP is considerable more comprehensive and rigorous than that used by CIRRPC. It should perhaps be noted that, for chronic exposure, the IREP screening doses are based on a linear model, whereas the screening doses from CIRRPC are based on a linear-quadratic model; in cases where the screening doses are large (small ERR), this leads to smaller CIRRPC screening doses than would have been obtained with a linear model.

APPENDIX F: Interactive RadioEpidemiological Program (IREP)

The Interactive RadioEpidemiological Program (IREP) is a web-based application that estimates the probability of causation (PC) as represented by the assigned share (AS) for an individual with a diagnosed disease who was exposed in the past to radiation. Throughout this text and online, the terms probability of causation and assigned share are used synonymously.

This program can be accessed online at the following address:

http://216.82.51.38/irep_nih

The initial screen of the IREP user interface is shown in Figure 1. IREP has been designed to accept inputs manually or through the use of an electronic input file. To initiate a calculation, the user is instructed to click on the appropriate button.

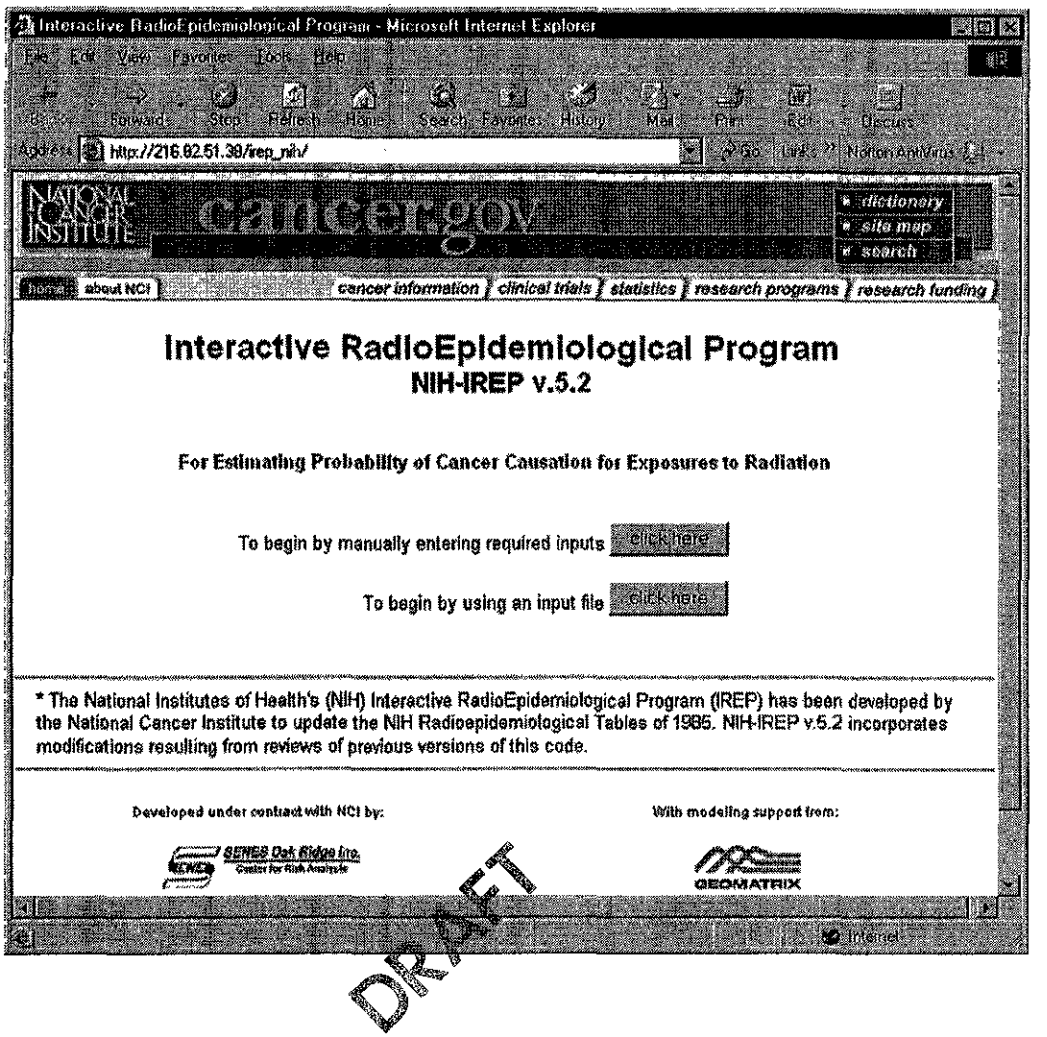


Figure 1. Initial screen of the IREP user interface

For a manual calculation using IREP, the user is requested to supply personal information (e.g. birth year, year of diagnosis, gender) and information about exposure (e.g. exposure year, organ equivalent dose, radiation type, duration of exposure). The main input screen is shown in Figure 2.

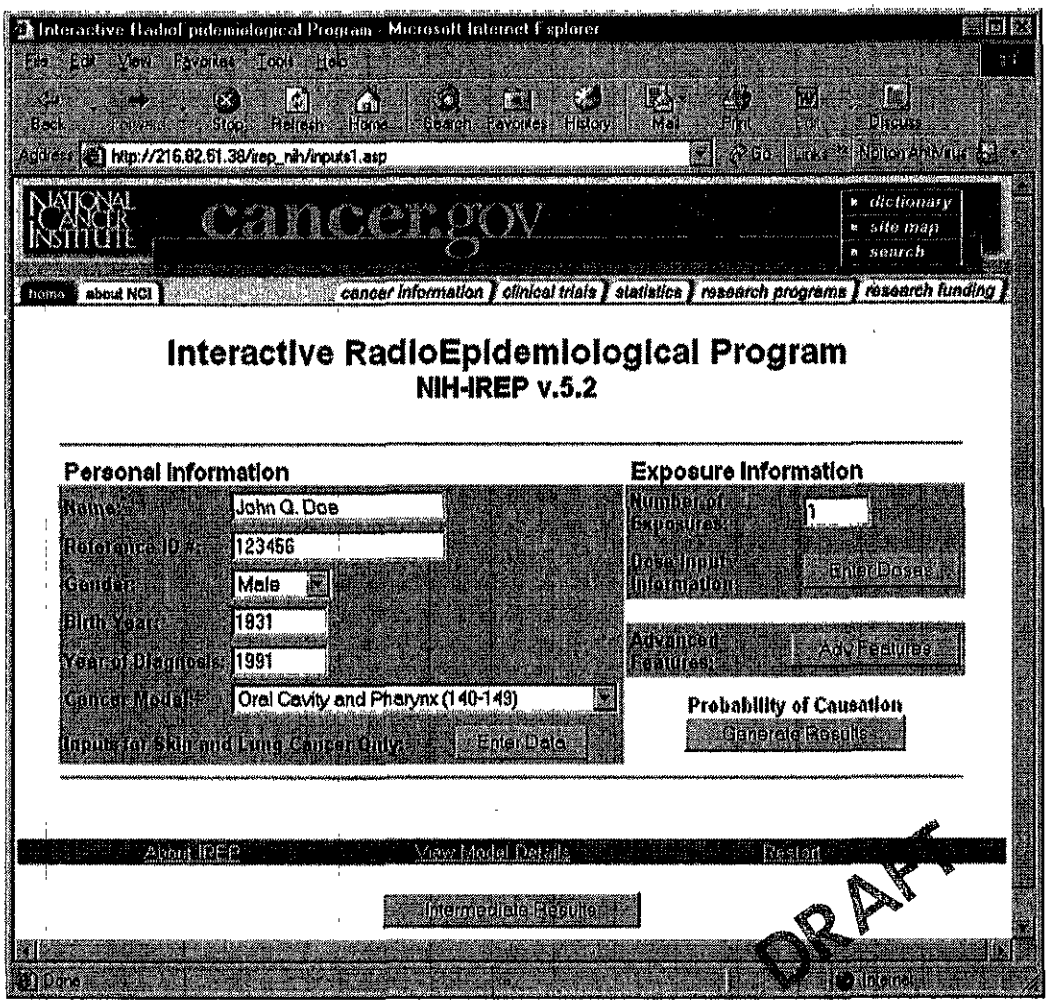


Figure 2. Main IREP input screen

After entering or uploading all requested input information, the probability of causation (assigned share) is estimated by a single mouse click on the button labeled "Generate Results" on the main input screen (Figure 2). The entered data will be submitted to a host computer where the underlying IREP code resides and *n* number of Monte Carlo iterations (using median Latin Hypercube sampling) will be performed. By default, the simulation sample size (*n*) is set to 1,000 iterations. The user can alter the number of Monte Carlo iterations and the initial random number seed by clicking the "Advanced Features" button located on the main input screen. The "Advanced Features" screen is shown in Figure 3.

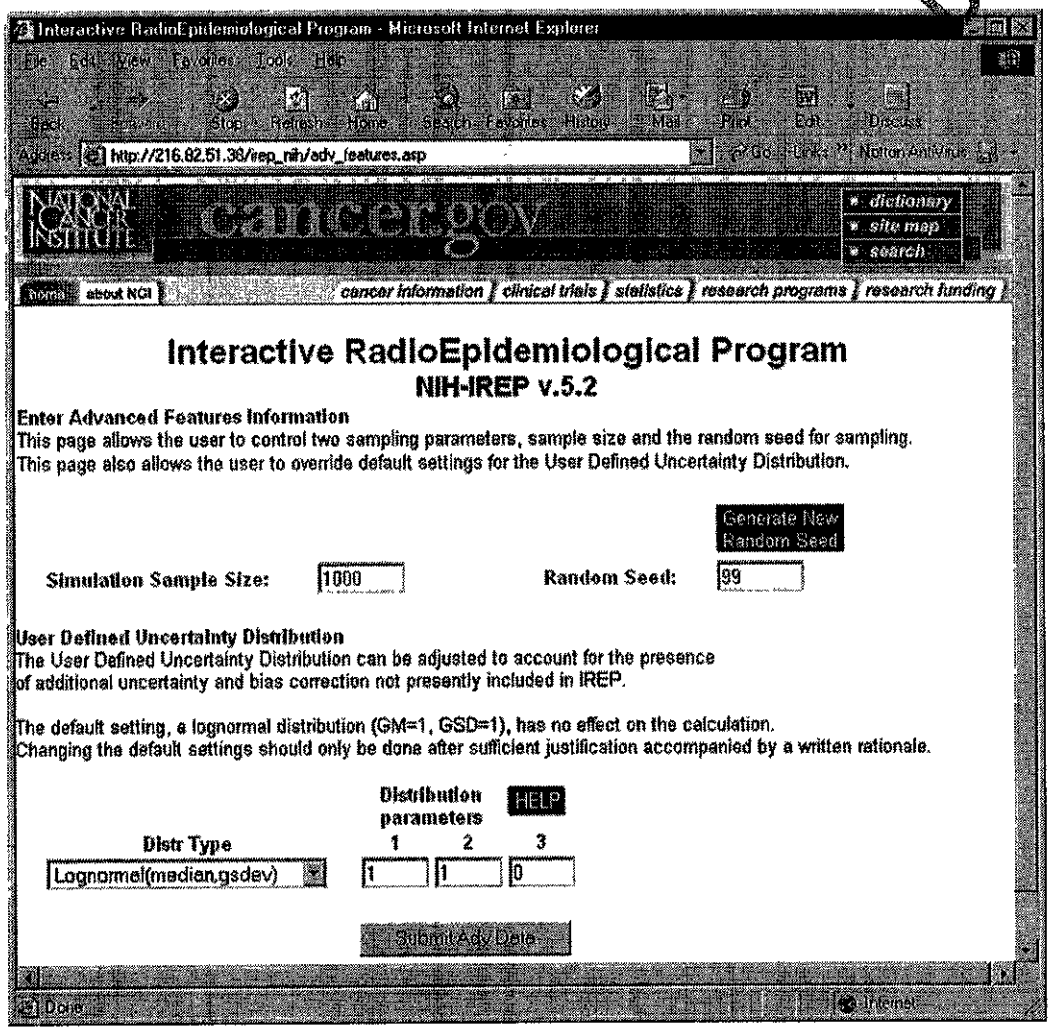
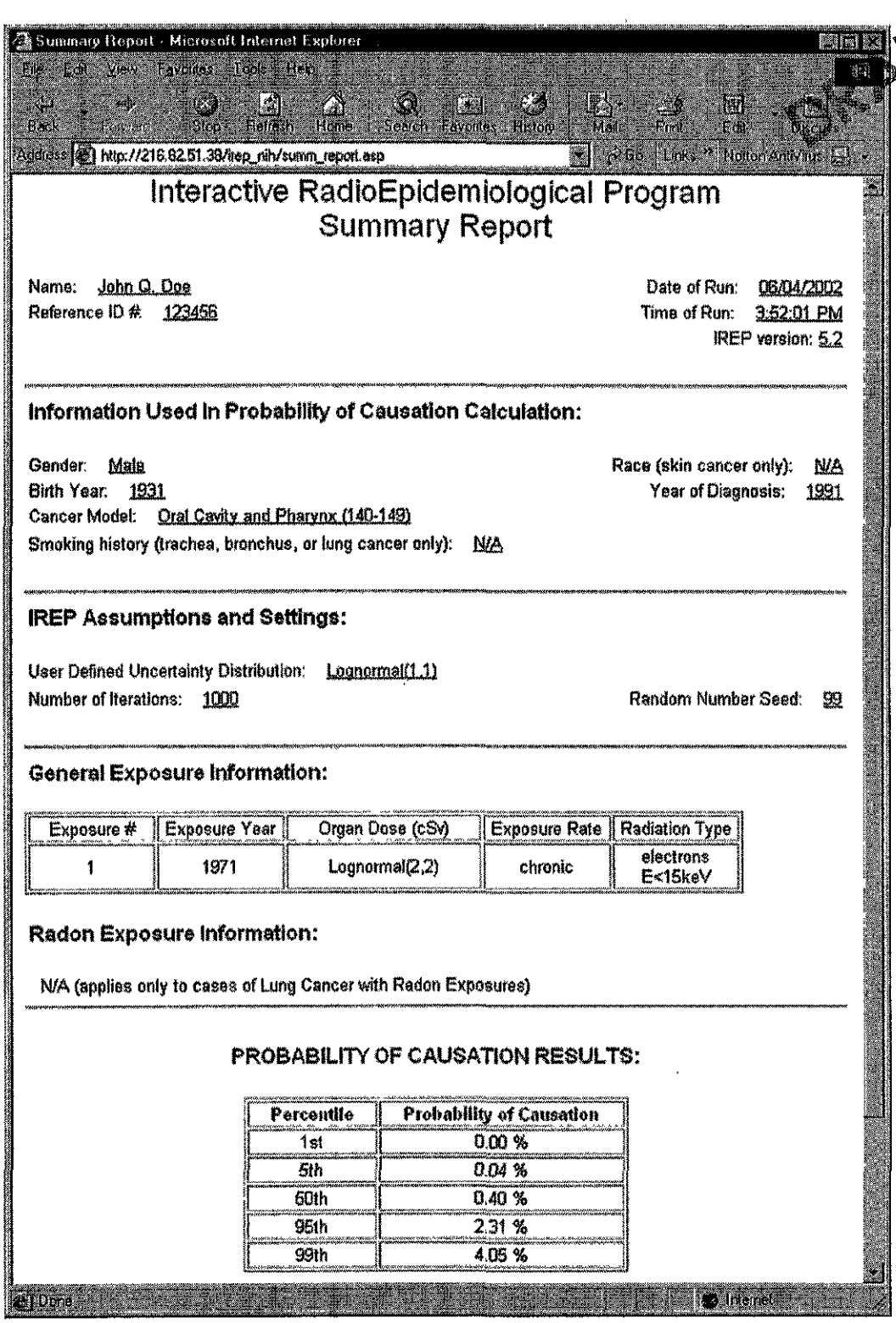


Figure 3. Advanced Features screen

A printable summary report (Figure 4) will be displayed by IREP. The report includes all input information required to estimate probability of causation.

To gain access to additional results, the user is instructed to click the "Intermediate Results" button at the bottom of the main IREP input screen. The intermediate results provided by IREP include: absorbed dose (cGy), the radiation effectiveness factor (REF) used in the calculation, the excess relative risk, and a series of importance analyses results showing the parameters that contribute most to the overall uncertainty in the estimate of probability of causation/assigned share.

For more information about the IREP computer code and its underlying assumptions and equations, click "View Model Details" in the bar across the bottom of the main input screen (as seen in Figure 2).



Interactive RadioEpidemiological Program
Summary Report

Name: John Q. Doe
Reference ID #: 123456

Date of Run: 06/04/2002
Time of Run: 3:52:01 PM
IREP version: 5.2

Information Used In Probability of Causation Calculation:

Gender: Male
Birth Year: 1931
Cancer Model: Oral Cavity and Pharynx (140-149)
Smoking history (trachea, bronchus, or lung cancer only): N/A

Race (skin cancer only): N/A
Year of Diagnosis: 1991

IREP Assumptions and Settings:

User Defined Uncertainty Distribution: Lognormal(1,1)
Number of Iterations: 1000

Random Number Seed: 99

General Exposure Information:

Exposure #	Exposure Year	Organ Dose (cSv)	Exposure Rate	Radiation Type
1	1971	Lognormal(2,2)	chronic	electrons E<15keV

Radon Exposure Information:

N/A (applies only to cases of Lung Cancer with Radon Exposures)

PROBABILITY OF CAUSATION RESULTS:

Percentile	Probability of Causation
1st	0.00 %
5th	0.04 %
50th	0.40 %
95th	2.31 %
99th	4.05 %

Figure 4. An example of the summary report produced by IREP

To utilize the input file option, a pre-formatted electronic file is required. A standardized electronic input file can be downloaded from the Internet by selecting the input file option on the initial screen of the IREP user interface. The "Upload Saved File" screen will appear (Figure 5); click "Download Template."

Once the standardized input file is downloaded, Microsoft Excel can be used to enter the personal and exposure information in the file. After saving the modified input file (with any desired file name), the input file can be uploaded into IREP by clicking the "Browse" button.

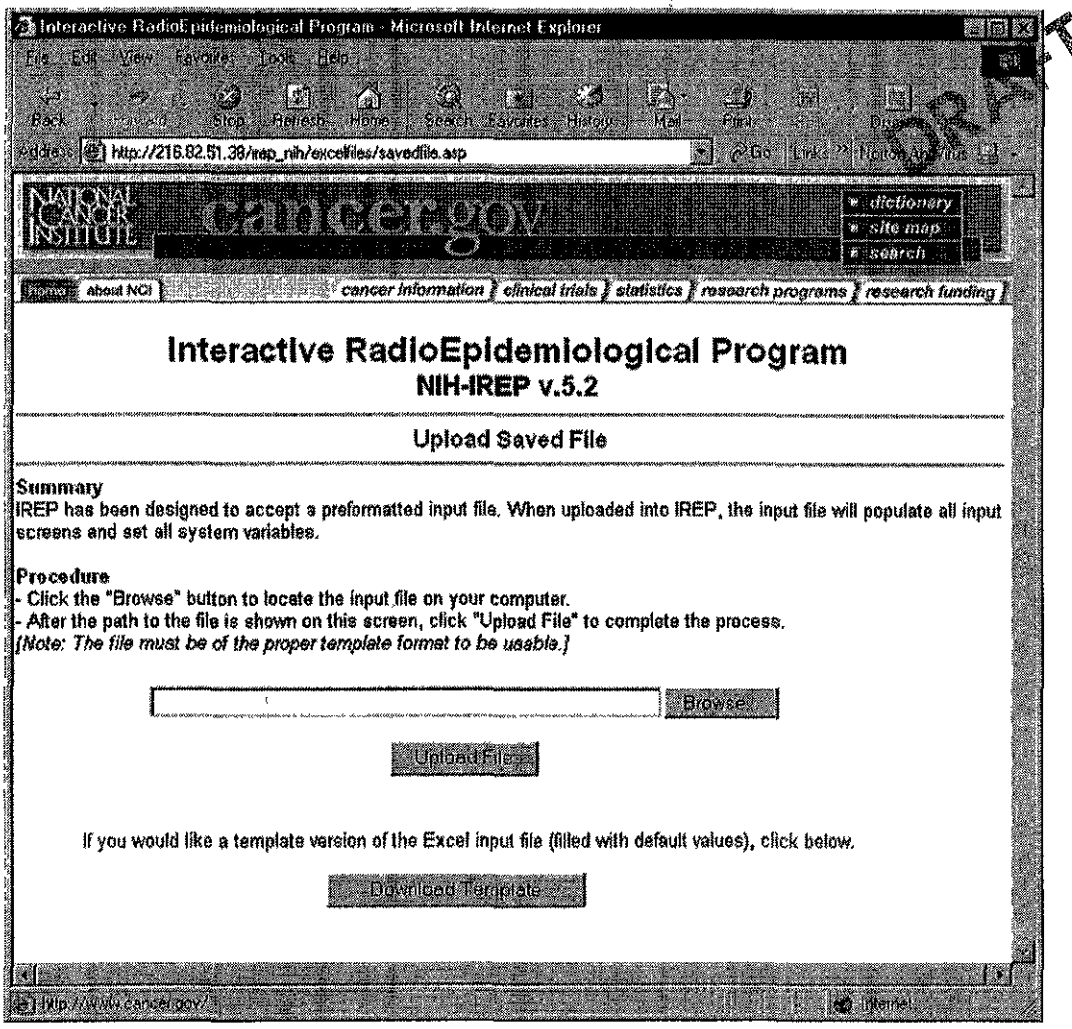


Figure 5. Upload Saved File screen

FIGURES

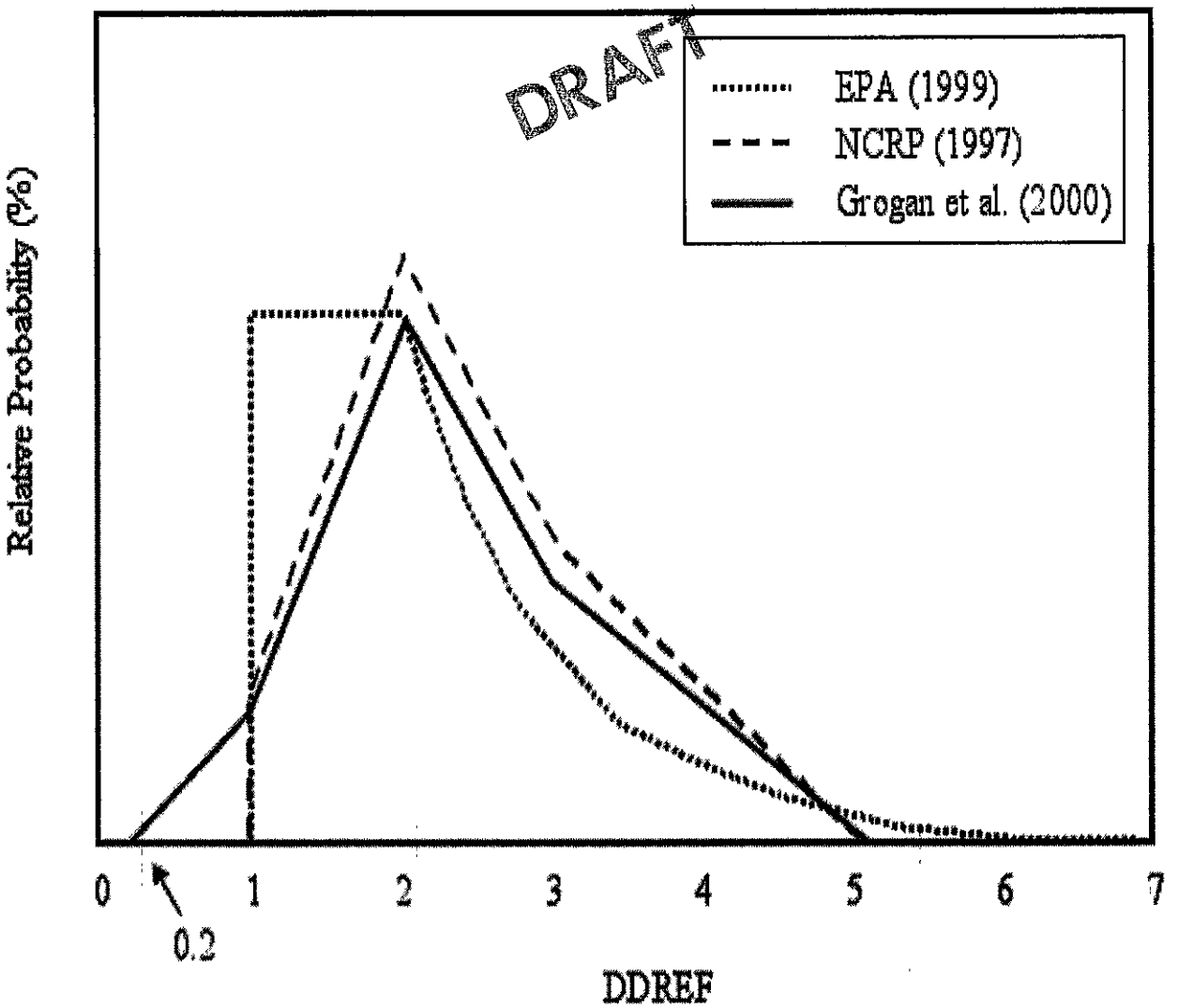


Figure IV.F.1. Probability distribution functions used by different authors to describe subjective uncertainty in the DDREF.

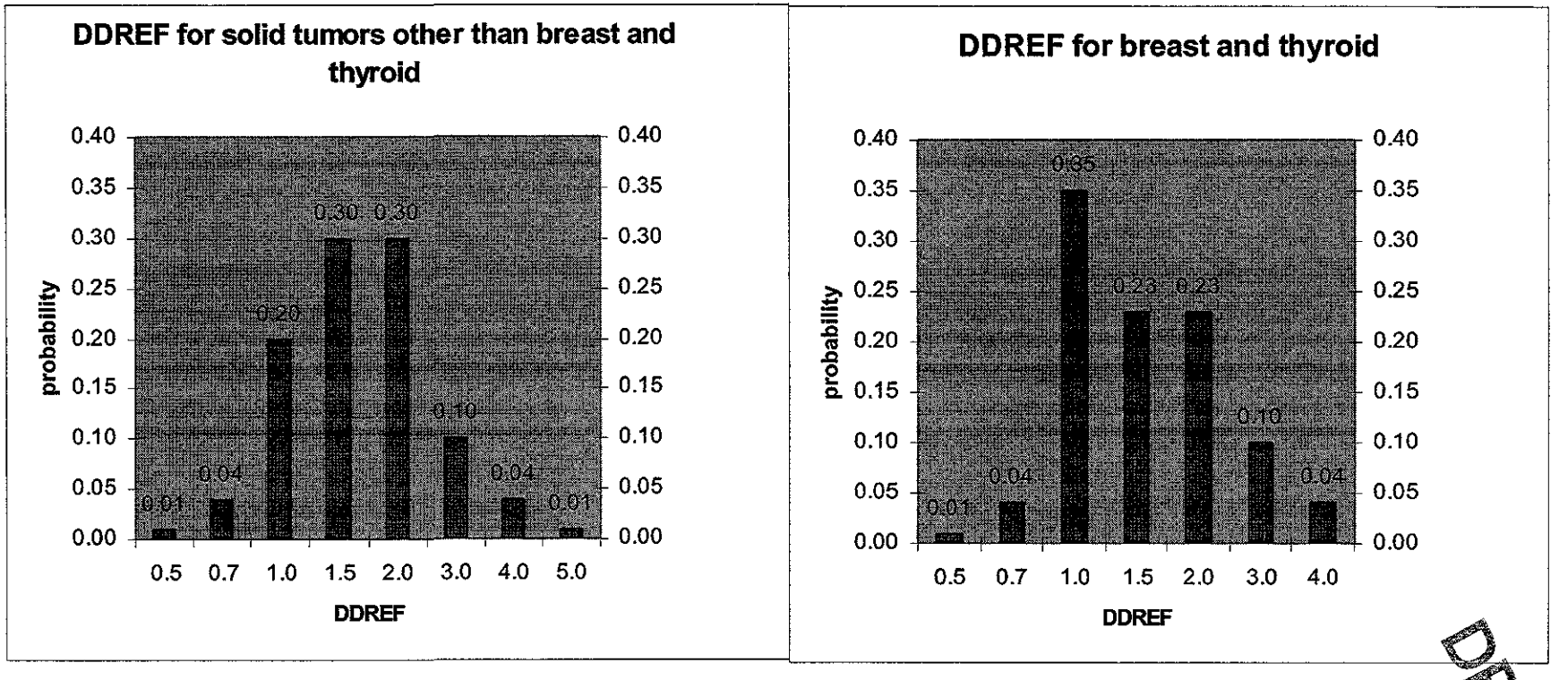


Figure IV.F.2. Subjective discrete probability distributions used in this report for the dose and dose-rate effectiveness factor applied to chronic exposures, for most solid cancers (left panel), and cancers of the thyroid gland and female breast (right panel).

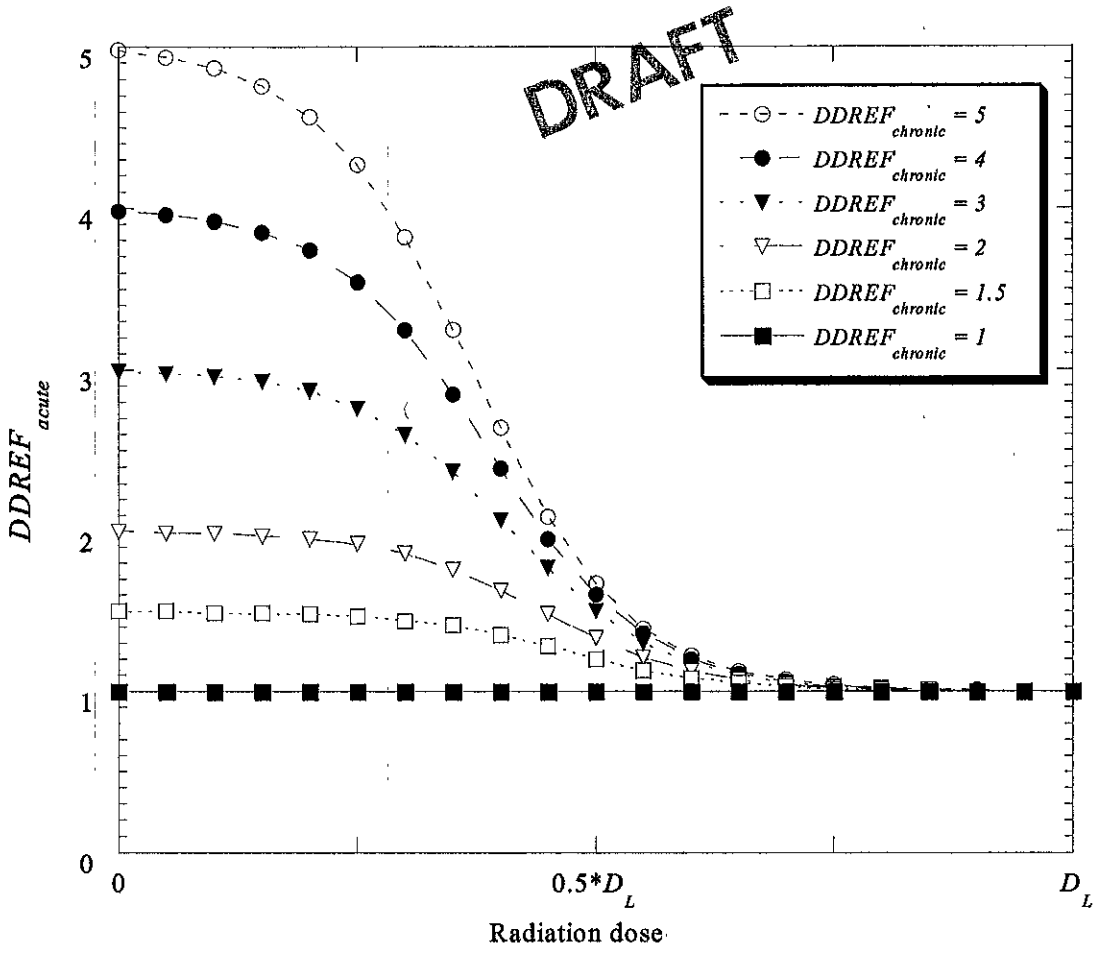


Figure IV.F.3. Variation of $DDREF_{acute}$ as a function of radiation dose for selected values of $DDREF_{chronic}$ for a fixed value of D_L, the lowest dose at which linearity of dose response is assumed to apply.

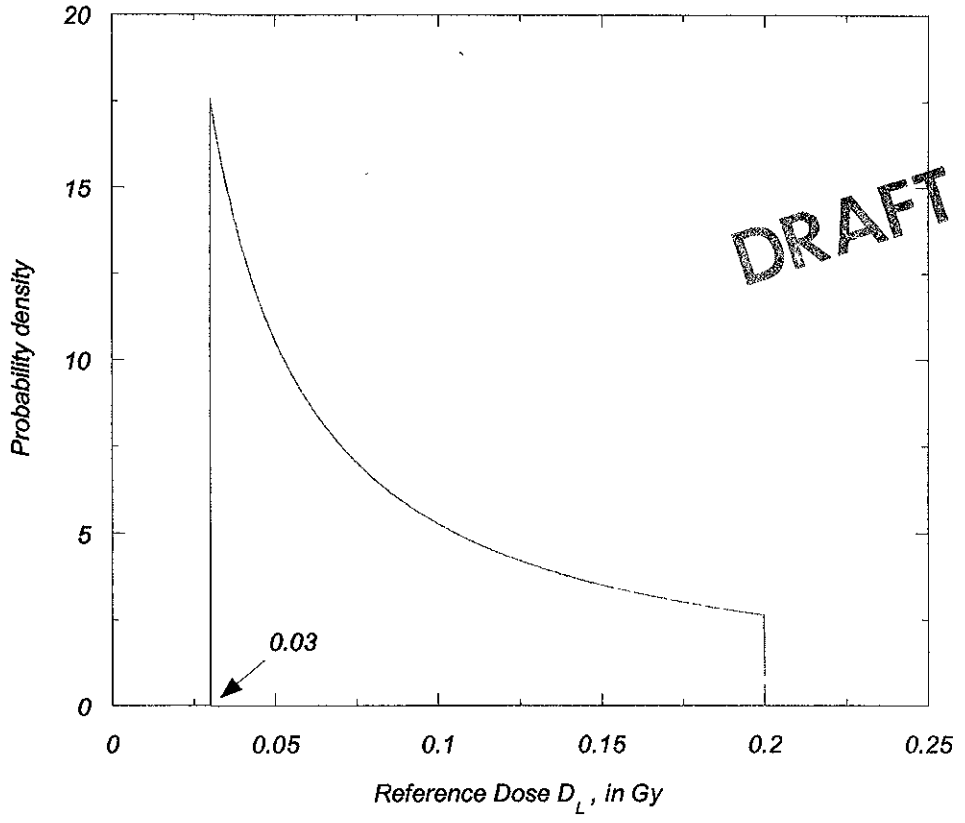


Figure IV.F.4.
Log-uniform uncertainty distribution of reference dose D_L, below which the DDREF applies.

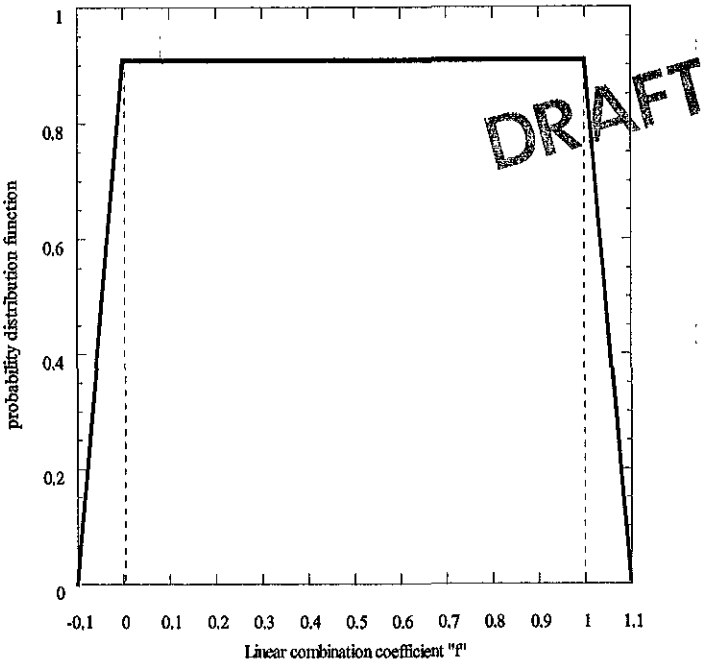


Figure IV.G.1 Probability density function assigned to the coefficient y for linear combination of the multiplicative (y=0) and additive (y=1) models for transfer of excess relative risk from one population to another, for most types of cancer.

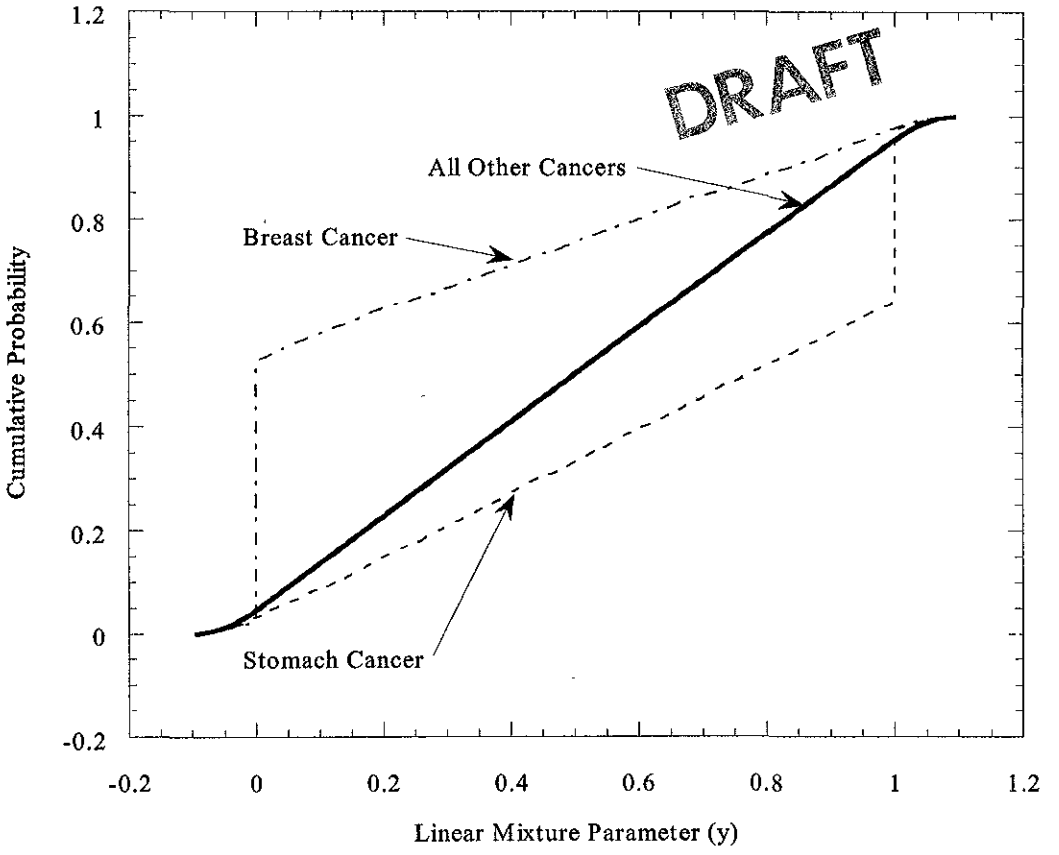
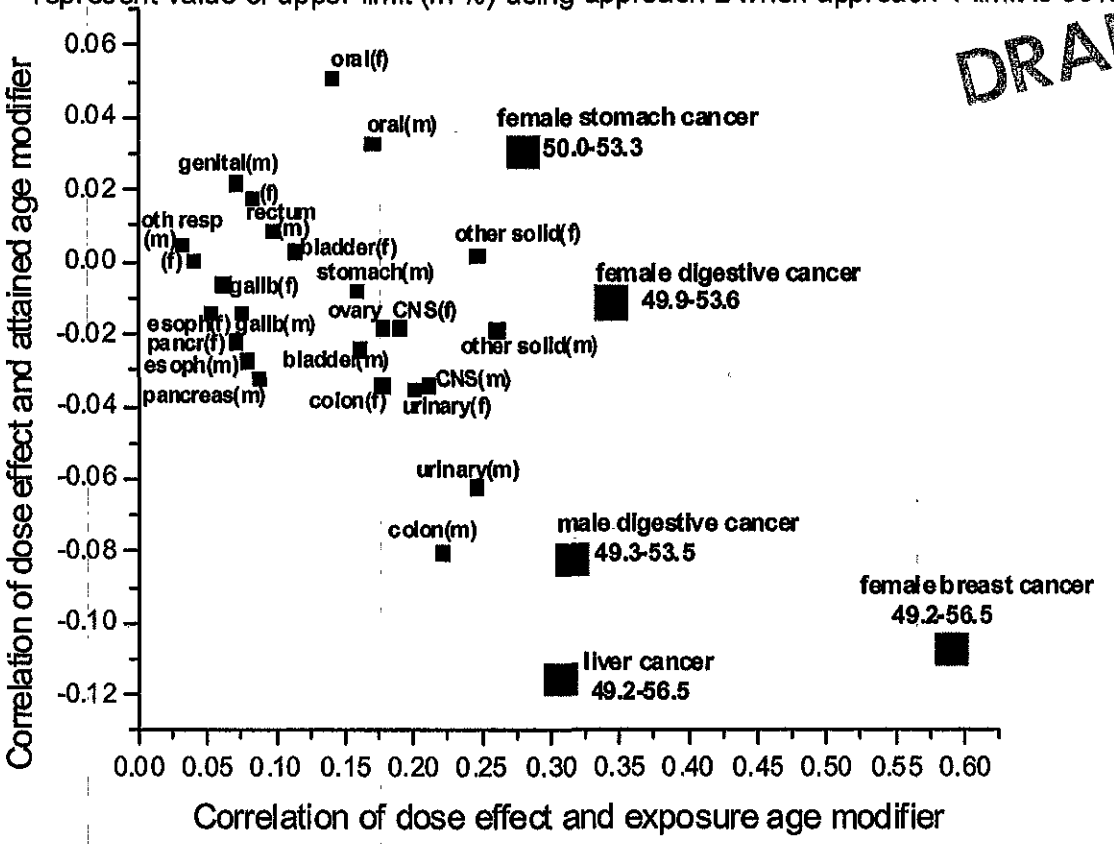


Figure IV.G.2 Cumulative distribution functions for the coefficient y used for computing a weighted average of the additive and multiplicative models for transfer between populations:

transfer model = y × multiplicative model + (1-y) × additive model.

Note that the transfer model for breast cancer places 50% probability on the model in Figure IV.F.1 and 50% on y=0, whereas for stomach cancer 33% is placed on y=1 and the remainder on the model in Figure IV.G.1. The multiplicative transfer model is used for thyroid cancer.

Appendix Figure C.1. Range of bias of 99% upper limit for AS, by correlation of dose and age effects. Bias ranges, given for approach 1 sites (large squares), represent value of upper limit (in %) using approach 2 when approach 1 limit is 50%.



TABLES

Table II.C.1. Cancer sites covered by the 1985 tables report.

Site/cancer	Source of coefficients	Comments
Leukemia	BEIR III	Absolute risk coefficient for total leukemia multiplied by 0.68 for AL, 0.32 for CGL
Bone and joint	BEIR III	Injected 224-Ra only
Salivary gland	Survey of published results (Land, 1984)	Exposure ages 0-14 only
Esophagus	BEIR III	
Stomach	BEIR III	
Colon	BEIR III	Exposure ages 20+ only
Liver	BEIR III	Exposure ages 20+ only
Pancreas	BEIR III	Exposure ages 20+ only
Lung	Low-LET radiation: Kato & Schull, 1982; high-LET radiation, Jacobi et al, 1987	Exposure ages 10+ only
Breast	Tokunaga et al, 1987	Linear dose response assumed; no effect of fractionation or protraction of dose
Kidney & bladder	BEIR III	Exposure ages 20+ only
Thyroid gland	LSS incidence study (Parker et al, 1973)	Linear dose response assumed; no effect of fractionation or protraction of dose

Table IV.C.1 Solid cancer sites covered by the LSS tumor registry report (Thompson, 1994), and their treatment in the present report.

Cancer site	Organ dose used	ICD-O site codes	Number of cases		Treatment in present report
			Exposed (≥10 mSv)	Non-exposed (<10 mSv)	
All solid tumors		140-165 170-195	4327	4286	Not calculated
Oral cavity and pharynx	Skin	140-149	64	68	Calculated as a group
Digestive system		150-159	2355	2442	Calculated as a group
Esophagus	Stomach	150	84	101	Calculated separately
Stomach	Stomach	151	1305	1353	Calculated separately
Colon	Intestine	153	223	234	Calculated separately
Rectum	Bladder	154	179	172	Calculated separately
Liver	Liver	155.0	283	302	Calculated separately
Gallbladder	Pancreas	155.1, 156	143	152	Calculated separately
Pancreas	Pancreas	157	122	118	Calculated separately
Other	Intestine	152, 158, 159	16	10	Use results for digestive system as a group
Respiratory system		160-165	528	499	Not calculated
Trachea, bronchus, and lung	Lung	162	449	423	Calculated separately
Nasal cavity	Skin	160	34	21	(Combined with other respiratory, non-lung cancers, and calculated as a group using lung dose)
Larynx	Lung	161	37	43	
Other	Lung	163-165	8	12	

Bone	Skeleton	170	4	11	Use results for other & ill-defined sites
Skin		173	97	84	Not calculated
Melanoma		173	6	7	Not calculated
Basal cell carcinoma	Skin	173	54	26	Dale Preston, personal communication
Other non-melanoma skin ca.	Skin	173	51	41	Dale Preston, personal communication
Female breast	Breast	174	289	240	Calculated separately
Female genital		179-184	430	461	Not calculated
Ovary	Ovary	183	66	67	Calculated separately
Uterus NOS	Uterus	179	47	39	(Combined with female
Uterine cervix	Uterus	180	265	288	genital cancers other than
Uterine corpus	Uterus	182	37	48	ovary, and calculated
Other	Uterus	181, 184	15	19	as a group)
Male genital		185-187	74	86	Calculated separately‡
Prostate	Bladder	185	61	79	(Uses risk estimates for male genital
Other	Testis	186, 187	13	7	group)
Urinary system		188-189	172	153	Calculated separately
Bladder	Bladder	188	115	95	Calculated separately
Kidney	Intestine	189.0	34	39	Uses risk estimates for urinary system
Renal pelvis and ureter	Intestine	189, 189.2	14	14	Uses risk estimates for urinary system
Other	Intestine	189.3-189.9	9	5	Uses risk estimates for urinary system
Nervous system	Brain	191, 192	69	56	Calculated separately
Thyroid	Thyroid	193	129	96	Based on data from Ron et al (1995)
Other and ill-defined sites (Residual solid cancers)	Intestine	170, 171, 175, 190, 194, 195	120	101	Calculated as a group

Table IV.C.2 Hematopoietic cancers covered by the LSS leukemia registry report (Preston, 1994), and their treatment in the present report (bone marrow dose was used for all types).

Cancer type	ICD-O site codes	Number of cases			Treatment in present report
		Exposed (≥10mSv)	Non-exposed	Total	
Leukemia, all types (except chronic lymphocytic leukemia)	204.0, 204.2 - 208	143	90	233	Calculated as a group
Acute myelogenous leukemia	205.0	60	43	103	Calculated separately
Acute lymphocytic leukemia	204.0	24	9	33	Calculated separately
Chronic myelogenous leukemia	205.1	41	17	58	Calculated separately
Lymphoma	201-202	86	105	191	Combined, and calculated as a group
Multiple myeloma	203	31	29	60	

Table IV.D.1. Computation of uncertainty distribution for ERR at 1 Sv. 1. Sites for which lognormal theory could be used with confidence to approximate the likelihood profile distribution for log(α), and for which default values of γ and δ were not used.*

Cancer site	log(α)	γ	δ	Var (log α)	Cov (log α , γ) *(correlation)*	Cov (log α.,δ) *(correlation)*	Var(γ)	Cov (γ, δ)	Var(δ)
All digestive Males	-1.590	-.0477	-1.622	0.10621	0.001868 *(0.314)*	-0.020011 *(-0.082)*	.0003332	-.007395	.56236
All digestive Females	-0.8614	-.0477	-1.622	0.05018	0.001403 *(0.343)*	-0.001882 *(-0.011)*	.0003332	-.007395	.56236
Stomach Females	-0.7998	-.04723	-1.781	0.07512	0.001380 *(0.279)*	0.006263 *(0.031)*	.0003252	-.007185	.54764
Liver Both sexes	-1.049	-.05204	-1.579	0.17108	0.002291 *(0.307)*	-0.03610 *(-0.115)*	.0003255	-.007347	.57368
Breast Females	0.02109	-.03722	-2.006	0.05456	0.002586 *(0.589)*	-0.01907 *(-0.107)*	.0003530	-.007934	.58018

* For exposure age $e \geq 30$ and attained age $a \geq 50$, log(ERR/Sv) is assumed to be normally distributed with mean log(α) and variance Var(log(α)). For other values of e and a, the log scale mean and variance are:

$$\text{mean} = \log(\alpha) + \gamma \times \min[\max(-15, e-30), 0] + \delta \times \min(\ln(a/50), 0);$$

$$\text{variance} = \text{var}(\log\alpha) + 2\times\text{cov}(\log\alpha,\gamma)\times\min[\max(-15,e-30),0] + 2\times\text{cov}(\log\alpha,\delta)\times\min(\ln(a/50),0) + \text{var}(\gamma)\times\min[\max(-15,e-30),0]^2$$
$$+2\times\text{cov}(\gamma,\delta)\times\min[\max(-15,e-30),0]\times\min(\ln(a/50),0) + \text{var}(\delta)\times\min(\ln(a/50),0)^2$$

Table IV.D.2 Computation of uncertainty distribution for ERR at 1 Sv. 2. Likelihood profile distributions for α, for exposure age e ≥ 30 and attained age $a \geq 50$: sites for which a lognormal approximation was not appropriate, and for which default values of γ and δ were used.*

Profile quantiles	Oral cavity and pharynx		Esophagus		Stomach	Colon		Rectum		Gall bladder		Pancreas	
	Males	Females	Males	Females	Males	Males	Females	Males	Females	Males	Females	Males	Females
0.9975	0.8004	1.765	1.216	3.253	0.3802	1.531	1.671	0.4946	1.078	0.5258	1.114	0.7062	1.510
0.995	0.7321	1.619	1.117	2.919	0.3516	1.429	1.567	0.4675	1.022	0.4725	1.013	0.6401	1.379
0.9875	0.6404	1.423	0.9820	2.492	0.3137	1.289	1.423	0.3946	0.8701	0.4013	0.8761	0.5509	1.201
0.975	0.5694	1.271	0.8755	2.179	0.2846	1.177	1.308	0.3413	0.7581	0.3465	0.7677	0.4815	1.060
0.95	0.4962	1.113	0.7634	1.869	0.2545	1.058	1.185	0.2888	0.6467	0.2905	0.6538	0.4095	0.9117
0.875	0.3935	0.8909	0.6025	1.450	0.2112	0.8852	1.005	0.2178	0.4917	0.2128	0.4893	0.3083	0.6984
0.8413	0.3651	0.8288	0.5563	1.324	0.1967	0.8357	0.9537	0.1951	0.4396	0.1921	0.4442	0.2802	0.6378
0.5	0.2055	0.4755	0.2905	0.6759	0.1184	0.5405	0.6430	0.0812	0.1875	0.0756	0.1805	0.1227	0.2871
0.1587	0.0907	0.2136	0.0784	0.1779	0.0497	0.3020	0.3857	<0	<0	<0	<0	<0	<0
0.125	0.0739	0.1736	0.0545	0.1229	0.0369	0.2672	0.3523	<0	<0	<0	<0	<0	<0
0.05	0.0308	0.0724	<0	<0	0.0051	0.1694	0.2463	<0	<0	<0	<0	<0	<0
0.025	0.0082	0.0190	<0	<0	<0	0.1134	0.1849	<0	<0	<0	<0	<0	<0
0.0125	<0	<0	<0	<0	<0	0.0671	0.1336	<0	<0	<0	<0	<0	<0
0.005	<0	<0	<0	<0	<0	0.0176	0.0772	<0	<0	<0	<0	<0	<0
0.0025	<0	<0	<0	<0	<0	<0	0.0409	<0	<0	<0	<0	<0	<0

Profile quantiles	Respiratory, non-lung		Urinary tract		Bladder		Ovary	Male genital	Central nervous system		Residual solid cancers		Lym-phoma*
	Males	Females	Males	Females	Males	Females	Females	Males	Males	Females	Males	Females	Both sexes
0.9975	0.7400	1.716	1.480	3.561	1.561	3.887	2.02	1.51	.9370	2.006	1.504	2.989	1.600
0.995	0.7009	1.619	1.396	3.354	1.474	3.577	1.86	1.44	0.8744	1.880	1.403	2.814	1.394
0.9875	0.5725	1.319	1.281	3.071	1.312	3.172	1.65	1.23	0.7444	1.618	1.267	2.575	1.134
0.975	0.4810	1.105	1.189	2.848	1.188	2.864	1.48	1.08	0.6491	1.424	1.160	2.385	0.9465
0.95	0.3930	0.9008	1.092	2.613	1.062	2.551	1.30	0.939	0.5553	1.230	1.048	2.185	0.7651
0.875	0.2755	0.6291	0.9489	2.273	0.8843	2.115	1.05	0.733	0.4295	0.9661	0.8887	1.893	0.5321
0.8413	0.2344	0.5366	0.9080	2.176	0.8311	1.987	0.982	0.667	0.3925	0.8862	0.8440	1.810	0.4742
0.5	0.0606	0.1377	0.6635	1.601	0.5388	1.282	0.576	0.3348	0.2057	0.4755	0.5859	1.315	0.1780
0.1587	≤0	<0	0.4650	1.137	0.3091	0.7337	0.267	0.0670	0.0759	0.1772	0.3883	0.9148	0.0142
0.125	≤0	<0	0.4380	1.073	0.2778	0.6587	0.230	0.0389	0.0600	0.1403	0.3626	0.8592	0.0032
0.05	≤0	<0	0.3571	0.8820	0.1869	0.4414	0.117	<0	0.0189	.04436	0.2871	0.6946	>0
0.025	≤0	<0	0.3102	0.7698	0.1352	0.3176	0.0569	<0	.00440	.01012	0.2445	0.5986	>0
0.0125	≤0	<0	0.2712	0.6759	0.0925	0.2159	<0	<0	<0	<0	0.2099	0.5187	>0
0.005	≤0	<0	0.2285	0.5716	0.0457	0.1057	<0	<0	<0	<0	0.1726	0.4305	>0
0.0025		<0	0.2011	0.5038	0.0173	0.0393	<0	<0	<0	<0	0.1492	0.3738	>0

* For exposure age $e < 30$ and/or attained age $a < 50$, α is multiplied by the uncertain age factor $f(e,a)$, which is assumed to be independent of α and lognormally distributed. The mean and variance of $\ln(f(e,a))$, which is assumed to be normally distributed, are as follows:

$$\text{mean} = -0.05255 \times \min[\max(-15, e-30), 0] - 1.626 \times \min(\ln(a/50), 0),$$

$$\text{variance} = 0.0003261 \times (\min[\max(-15, e-30), 0])^2 - 0.007297 \times \min[\max(-15, e-30), 0] \times \min(\ln(a/50), 0) + 0.5648 \times [\min(\ln(a/50), 0)]^2.$$

Table IV.D.3 Computation of uncertainty distribution for ERR at 1 Sv. 3. Likelihood profile distributions for α, for all exposure ages and attained ages: sites for which a lognormal approximation was not appropriate for the statistical uncertainty distribution for α, and for which $\gamma=0$ and $\delta=0$ were assumed.

Profile quantiles	Lung		Female genital less ovary
	Males	Females	Females
0.9975	1.114	3.449	0.172
0.995	1.053	3.307	0.136
0.9875	0.9680	3.109	0.0866
0.975	0.8987	2.948	0.0791
0.95	0.8237	2.775	0.0607
0.875	0.7112	2.516	0.0463
0.8413	0.6783	2.441	0.0030
0.5	0.4740	1.973	-0.189
0.1587	0.2953	1.563	-0.278
0.125	0.2681	1.504	-0.289
0.05	0.1885	1.323	>0
0.025	0.1408	1.214	>0
0.0125	0.1000	1.119	>0
0.005	0.0537	1.012	>0
0.0025	0.0239	0.9406	>0

Table IV.D.4. Computation of uncertainty distribution for ERR at 1 Sv. 4. Leukemia other than chronic lymphocytic, combined sexes: Likelihood profile distributions, by representative values for exposure age and time since exposure.

Profile quantiles	Exposure age 20						Exposure age 30					
	5 yr	10 yr	15 yr	25 yr	35 yr	45 yr	5 yr	10 yr	15 yr	25 yr	35 yr	45 yr
0.9975	72.69	29.87	13.54	3.967	1.671	0.8029	37.55	18.19	9.412	3.361	1.672	0.9342
0.995	65.99	27.68	12.71	3.744	1.538	0.7102	34.69	17.09	8.944	3.206	1.556	0.8387
0.9875	57.46	24.83	11.62	3.438	1.358	0.5913	30.97	15.62	8.311	2.991	1.400	0.7154
0.975	51.20	22.68	10.78	3.194	1.217	0.5038	28.16	14.49	7.816	2.818	1.277	0.6239
0.95	45.05	20.51	9.922	2.934	1.071	0.4180	25.33	13.33	7.299	2.633	1.149	0.5334
0.875	36.94	17.57	8.719	2.554	0.8658	0.3065	21.47	11.70	6.559	2.358	0.9676	0.4137
0.8413	34.80	16.76	8.385	2.445	0.8091	0.2778	20.42	11.25	6.350	2.278	0.9168	0.3820
0.5	23.55	12.35	6.481	1.784	0.4911	0.1352	14.65	8.662	5.121	1.789	0.6253	0.2185
0.1587	16.10	9.173	5.015	1.239	0.2730	0.0585	10.52	6.674	4.124	1.366	0.4060	0.1173
0.125	15.21	8.776	4.824	1.168	0.2480	0.0511	10.01	6.416	3.991	1.308	0.3786	0.1062
0.05	12.65	7.592	4.244	0.9509	0.1783	0.0320	8.481	5.633	3.580	1.127	0.2979	0.0755
0.025	11.25	6.925	3.907	0.8277	0.1428	0.0234	7.627	5.180	3.338	1.019	0.2535	0.0601
0.0125	10.14	6.380	3.627	0.7271	0.1161	0.0175	6.933	4.804	3.134	0.9281	0.2181	0.0486
0.005	8.959	5.788	3.315	0.6185	0.0898	0.0123	6.184	4.389	2.905	0.8259	0.1809	0.03
0.0025	8.227	5.412	3.113	0.5503	0.0745	0.0095	5.709	4.120	2.754	0.7591	0.1581	0.03

Table IV.D.5. Computation of uncertainty distribution for ERR at 1 Sv. 5. Acute lymphocytic leukemia, combined sexes: Likelihood profile distributions, by exposure age and time since exposure.

Profile quantiles	Exposure age < 20									Exposure age≥20
	5 yr	10 yr	15 yr	20 yr	25 yr	30 yr	35 yr	40 yr	45 yr	>5 yr
0.9975	701.7	200.8	67.53	28.30	14.29	8.290	5.268	3.53	2.450	11.33
0.995	588.5	171.7	58.43	24.50	12.25	6.957	4.284	2.770	1.840	9.970
0.9875	456.8	137.3	47.48	19.89	9.761	5.347	3.133	1.907	1.188	8.277
0.975	369.5	114.0	39.93	16.66	8.016	4.241	2.373	1.371	0.806	7.068
0.95	291.8	92.82	32.93	13.64	6.383	3.230	1.708	0.926	0.509	5.909
0.875	202.0	67.56	24.37	9.876	4.372	2.039	0.9773	0.4743	0.2332	4.426
0.8413	180.3	61.32	22.20	8.913	3.864	1.751	0.8125	0.3877	0.1835	4.038
0.5	86.69	32.91	11.99	4.342	1.570	0.5679	0.2053	0.0742	0.02679	2.117
0.1587	41.68	17.81	6.167	1.810	0.4935	0.1263	0.02979	0.00846	0.00241	0.9546
0.125	37.68	16.34	5.557	1.566	0.4102	0.1042	0.02524	0.00649	0.00159	0.8295
0.05	26.27	12.10	3.803	0.9047	0.1964	0.0413	0.008466	0.00175	0.00035	0.4806
0.025	20.90	9.989	2.908	0.6069	0.1149	0.0210	0.003768	0.00066	0.00012	0.3074
0.0125	17.01	8.405	2.231	0.4054	0.06711	0.0107	0.001663	0.00026	0.00004	0.1803
0.005	13.30	6.828	1.561	0.2348	0.03213	0.00424	.0005558	0.00007	0.00001	.0602
0.0025	11.21	5.903	1.177	0.1523	0.01814	0.00209	.0002290	0.00003	0.000003	

Table IV.D.6. Computation of uncertainty distribution for ERR at 1 Sv. 6. Acute myelogenous leukemia, combined sexes: Likelihood profile distributions, by time since exposure.

Profile quantiles	Time since exposure									
	5 yr	10 yr	15 yr	20 yr	25 yr	30 yr	35 yr	40 yr	45 yr	50 yr
0.9975	28.57	16.54	10.10	6.666	4.903	4.071	3.707	3.563	3.527	3.550
0.995	25.57	15.12	9.385	6.266	4.627	3.819	3.428	3.232	3.129	3.075
0.9875	21.79	13.28	8.443	5.729	4.253	3.478	3.057	2.802	2.626	2.493
0.975	19.05	11.91	7.727	5.314	3.959	3.210	2.771	2.479	2.261	2.085
0.95	16.40	10.55	7.001	4.884	3.651	2.931	2.477	2.157	1.907	1.701
0.875	12.96	8.719	5.997	4.277	3.208	2.530	2.067	1.722	1.450	1.228
0.8413	12.06	8.229	5.722	4.108	3.082	2.416	1.953	1.605	1.331	1.110
0.5	7.453	5.579	4.176	3.126	2.340	1.752	1.311	0.9810	0.7346	0.5499
0.1587	4.548	3.742	3.024	2.356	1.734	1.217	0.8329	0.5627	0.3776	0.2523
0.125	4.215	3.518	2.877	2.255	1.653	1.147	0.7734	0.5140	0.3390	0.2226
0.05	3.267	2.860	2.435	1.947	1.401	0.9314	0.5961	0.3745	0.2329	0.1440
0.025	2.765	2.497	2.183	1.768	1.252	0.8064	0.4978	0.3010	0.1800	0.1069
0.0125	2.374	2.206	1.976	1.618	1.126	0.7024	0.4188	0.2443	0.1408	0.0806
0.005	1.972	1.895	1.749	1.453	0.9829	0.5880	0.3354	0.1870	0.1029	0.0562
0.0025	1.728	1.700	1.603	1.345	0.8885	0.5146	0.2839	0.1531	0.0815	0.0430

Table IV.D.7. Computation of uncertainty distribution for ERR at 1 Sv. 7. Chronic myelogenous leukemia: Likelihood profile distributions, by sex and time since exposure.

Profile quantiles	Time since exposure									
	5	10	15	20	25	30	35	40	45	50
Males										
0.9975	134.6	34.15	14.49	7.474	4.262	2.573	1.606	1.023	0.6598	0.4290
0.995	120.7	30.82	12.86	6.480	3.588	2.091	1.254	0.7654	0.4720	0.2931
0.9875	103.0	26.62	10.82	5.242	2.762	1.519	0.8548	0.4875	0.2803	0.1620
0.975	90.12	23.56	9.337	4.355	2.187	1.138	0.6030	0.3230	0.1742	0.09427
0.95	77.60	20.58	7.899	3.506	1.655	0.8031	0.3954	0.1962	0.09779	0.04890
0.875	61.29	16.67	6.021	2.428	1.020	0.4363	0.1881	0.08147	0.03539	0.01540
0.8413	57.03	15.64	5.528	2.155	0.8702	0.3565	0.1470	0.06087	0.02526	0.01050
0.5	35.09	10.19	2.960	0.8598	0.2497	0.0725	0.0211	0.006119	0.001777	0.00052
0.1587	21.24	6.515	1.354	0.2548	0.04696	0.00859	0.00157	0.0002850	0.000052	0.00001
0.125	19.66	6.071	1.182	0.2057	0.03498	0.00590	0.00099	0.0001664	0.000028	0.000005
0.05	15.18	4.764	0.7191	0.09384	0.01191	0.00150	0.00019	0.00002	0.000003	0
0.025	12.81	4.038	0.5020	0.05319	0.00547	0.00056	0.00006	0.000006	0	0
0.0125	10.98	3.450	0.3518	0.03034	0.00254	0.00021	0.00002	0.000001	0	0
0.005	9.105	2.814	0.2193	0.01440	0.000918	0.00006	0.000004	0	0	0
0.0025	7.972	2.412	0.1523	0.00812	0.000420	0.00002	0.000001	0	0	0

Females										
0.9975	46.16	31.20	23.24	18.77	16.29	15.08	14.83	15.44	16.95	19.56
0.995	40.32	27.45	20.49	16.54	14.31	13.18	12.87	13.24	14.30	16.12
0.9875	33.14	22.87	17.14	13.83	11.91	10.87	10.48	10.58	11.13	12.10
0.975	28.06	19.63	14.79	11.92	10.22	9.259	8.804	8.728	8.957	9.443
0.95	23.24	16.55	12.55	10.12	8.630	7.733	7.231	7.003	6.973	7.086
0.875	17.18	12.64	9.728	7.851	6.625	5.813	5.265	4.886	4.614	4.411
0.8413	15.64	11.63	9.003	7.269	6.112	5.323	4.768	4.361	4.048	3.796
0.5	8.040	6.543	5.325	4.334	3.527	2.871	2.336	1.901	1.547	1.259
0.1587	3.697	3.385	3.000	2.500	1.919	1.393	0.9830	0.6838	0.4718	0.3239
0.125	3.239	3.027	2.729	2.289	1.736	1.231	0.8466	0.5729	0.3843	0.2563
0.05	2.005	2.020	1.948	1.686	1.212	0.7861	0.4901	0.2998	0.1815	0.1092
0.025	1.410	1.501	1.526	1.366	0.9354	0.5658	0.3280	0.1865	0.1048	0.0585
0.0125	0.9859	1.109	1.192	1.115	0.7207	0.4049	0.2181	0.1151	0.06011	0.0312
0.005	0.5983	0.7262	0.8444	0.8553	0.5006	0.2530	0.1229	0.05860	0.02765	0.0130
0.0025	0.3972	0.5123	0.6350	0.6968	0.3686	0.1702	0.07589	0.03326	0.01444	0.00623

Table IV.D.8. Computation of uncertainty distribution for ERR at 1 Sv. 8. Thyroid cancer, combined sexes: Lognormal theory geometric mean (GM) and geometric standard deviation (GSD), by exposure age.

Exposure age	GM	GSD
0	9.463	1.290
5	6.262	1.229
10	4.136	1.277
15	2.732	1.409
20	1.804	1.591
25	1.192	1.812
30	0.788	2.074
35	0.521	2.379
40	0.345	2.732
45	0.228	3.140
50	0.151	3.611

Table IV.D.9. Computation of uncertainty distribution for ERR at 1 Sv. 9. Likelihood profile distributions for non-melanoma skin cancer, both sexes combined. Basal cell carcinoma: exposure ages 0-9, 20, 30, and 40 or older, and all attained ages; for intermediate ages at exposure, logarithms of specific quantiles are to be interpolated by age. Other non-melanoma skin cancers: combined sexes, all exposure ages and all attained ages.

Profile quantiles	Basal cell skin cancer, by age at exposure				Other non-melanoma skin cancer
	0-9.99	20	30	≥40	
0.9975	149.7	23.79	5.872	2.342	0.8243
0.995	129.1	21.34	5.360	2.095	0.7156
0.9875	104.3	18.26	4.687	1.773	0.5715
0.975	87.30	16.02	4.175	1.531	0.4613
0.95	71.53	13.84	3.655	1.288	0.3489
0.875	52.35	11.01	2.938	0.9613	0.1940
0.8413	47.61	10.27	2.742	0.8744	0.1519
0.5	25.22	6.441	1.645	0.4200	-0.08068
0.1587	13.14	3.970	0.8365	0.1495	<0
0.125	11.88	3.677	0.7399	0.1235	<0
0.05	8.467	2.837	0.4556	0.0579	<0
0.025	6.778	2.376	0.3132	0.0323	<0
0.0125	5.524	1.998	0.2125	0.0178	<0
0.005	4.295	1.576	0.1245	0.0078	<0
0.0025	3.584	1.301	0.0814	0.0041	<0

Table IV.D.10. Likelihood profiles for $ERR_{1\ wlm}$ for radon-related lung cancer, by smoking history, age at diagnosis, and time since last exposure. ERR is assumed to be linear in $wlm^{0.82}$, where *wlm* is cumulative radon exposure in working level months.

Profile quantiles	Age ≤ 45 at diagnosis			Age 63 at diagnosis			Age ≥75 at diagnosis		
	Time since last exposure:			Time since last exposure:			Time since last exposure:		
	≤ 5 years	15 years	≥ 25 years	≤ 5 years	15 years	≥ 25 years	≤ 5 years	15 years	≥ 25 years
Smokers									
0.9975	6.73608	2.2048	0.771368	0.629928	0.196976	0.06683	0.22048	0.067267	0.022121
0.995	5.33416	1.7472	0.608608	0.521352	0.163592	0.055349	0.178776	0.054798	0.018013
0.9875	3.81576	1.25008	0.432952	0.396552	0.125112	0.042172	0.13208	0.040799	0.013406
0.975	2.88392	0.945672	0.325624	0.314912	0.099798	0.03355	0.102346	0.031845	0.010462
0.95	2.1112	0.693056	0.23712	0.243152	0.07749	0.025969	0.076887	0.024128	0.00793
0.875	1.3	0.427128	0.144664	0.161616	0.052	0.017337	0.048974	0.01559	0.005126
0.8413	1.12216	0.368992	0.124592	0.142792	0.046093	0.015309	0.042661	0.013645	0.004487
0.5	0.414544	0.136552	0.04498	0.060788	0.02002	0.006597	0.0169	0.005569	0.001835
0.1587	0.163072	0.05381	0.017243	0.025574	0.008601	0.0028	0.006397	0.002182	0.000719
0.125	0.141232	0.046613	0.014872	0.02236	0.007544	0.002451	0.005542	0.001891	0.000623
0.05	0.087953	0.029078	0.009145	0.014279	0.004868	0.001571	0.003384	0.001171	0.000385
0.025	0.06501	0.021518	0.006702	0.01067	0.003662	0.001177	0.002454	0.000857	0.000282
0.0125	0.049566	0.016422	0.005073	0.008191	0.002828	0.000906	0.001835	0.000646	0.000212
0.005	0.035849	0.011898	0.003638	0.005947	0.002069	0.000659	0.001289	0.000458	0.00015
0.0025	0.02861	0.009508	0.002887	0.004747	0.00166	0.000528	0.001006	0.00036	0.000118

Nonsmokers									
0.9975	25.2603	8.268	2.89263	0.655125	0.204855	0.069504	0.229299	0.069958	0.023006
0.995	20.0031	6.552	2.28228	0.542206	0.170136	0.057563	0.185927	0.05699	0.018733
0.9875	14.3091	4.6878	1.62357	0.412414	0.130116	0.043859	0.137363	0.042431	0.013942
0.975	10.8147	3.54627	1.22109	0.327508	0.10379	0.034892	0.10644	0.033119	0.010881
0.95	7.917	2.59896	0.8892	0.252878	0.08059	0.027008	0.079963	0.025093	0.008247
0.875	4.875	1.60173	0.54249	0.168081	0.05408	0.01803	0.050933	0.016213	0.005331
0.8413	4.2081	1.38372	0.46722	0.148504	0.047937	0.015921	0.044367	0.014191	0.004666
0.5	1.55454	0.51207	0.168675	0.06322	0.020821	0.006861	0.017576	0.005792	0.001908
0.1587	0.61152	0.201786	0.064662	0.026597	0.008945	0.002912	0.006653	0.002269	0.000748
0.125	0.52962	0.174798	0.05577	0.023254	0.007846	0.002549	0.005764	0.001966	0.000648
0.05	0.329823	0.109044	0.034293	0.01485	0.005063	0.001634	0.00352	0.001218	0.000401
0.025	0.243789	0.080691	0.025132	0.011097	0.003808	0.001224	0.002553	0.000891	0.000293
0.0125	0.185874	0.061581	0.019024	0.008519	0.002941	0.000942	0.001908	0.000671	0.000221
0.005	0.134433	0.044616	0.013642	0.006185	0.002151	0.000686	0.00134	0.000476	0.000156
0.0025	0.107289	0.035654	0.010826	0.004936	0.001726	0.000549	0.001046	0.000374	0.000123

Table IV.H.1. Photons and electrons: Summary of probability distributions of radiation effectiveness factors to be used in estimating cancer risks and assigned shares in accordance with eq. (IV.H.1), (IV.H.3), or (IV.H.4)[a]

Radiation type	Exposure	Probability distribution of radiation effectiveness factor (REF_L)
Photons	Chronic or acute[b]	
E > 250 keV		Single-valued at 1.0 (higher-energy photons are assumed reference radiation)
E = 30-250 keV		Hybrid distribution with – 25% probability assigned to value 1.0; 75% probability assigned to lognormal distribution with 95% confidence interval between 1.0 and 5.0
E < 30 keV		Product of two distributions – (1) hybrid distribution for E = 30-250 keV; and (2) triangular distribution with minimum of 1.0, mode of 1.3, and maximum of 1.6
Electrons	Chronic or acute[b]	
E > 15 keV		Single-valued at 1.0 (assumed to be same as value for reference higher-energy photons)
E < 15 keV[c]		Lognormal distribution with 95% confidence interval between 1.2 and 5.0

[a]The equations are given in Section IV.H of the report. Equation (IV.H.1) applies to solid tumors, eq. (IV.H.3) applies to leukemias under conditions of chronic exposure, and eq. (IV.H.4) applies to leukemias under conditions of acute exposure.

[b]When eq. (IV.H.1) is used, DDREF is always applied under conditions of chronic exposure. At acute doses greater than 0.2 cGy, DDREF is assumed to be 1.0. At acute doses less than 0.2 cGy, a DDREF that can exceed 1.0 is applied, and the distribution of possible values approaches the probability distribution of DDREF that applies to all chronic exposures as the dose approaches zero.

[c]Probability distribution is based on data on RBE for low-energy beta particles emitted in decay of tritium (^3H); distribution is applied to other electrons of energy less than 15 keV, except low-energy Auger electrons emitted by radionuclides that are incorporated into DNA are excluded.

Table IV.H.2. Alpha particles: Summary of probability distributions of radiation effectiveness factors to be used in estimating cancer risks and assigned shares in accordance with eq. (IV.H.1) or (IV.H.3)[a]

Cancer type	Exposure	Probability distribution of radiation effectiveness factor (REF_L)
Leukemias[b]	Chronic[c]	
All energies of alpha particles		Hybrid distribution with – 25% probability assigned to value 1.0; 50% probability assigned to lognormal distribution with 95% confidence interval between 1.0 and 15; 25% probability assigned to lognormal distribution with 95% confidence interval between 2.0 and 60[d]
Solid tumors	Chronic[c]	
All energies of alpha particles		Lognormal distribution with 95% confidence interval between 3 and 80
Correction for inverse dose-rate effect for all exposures to alpha particles – Discrete distribution with – 70% probability assigned to value 1.0; 20% probability assigned to value 1.5; 7.5% probability assigned to value 2.0; 2.5% probability assigned to value 3.0		

[a]The equations are given in Section IV.H of the report. Equation (IV.H.1) applies to solid tumors, and eq. (IV.H.3) applies to leukemias.

[b]Assumed probability distribution applies to leukemias, lymphomas, and lymphocytic cancers.

[c]Acute exposures to alpha particles emitted by radionuclides generally should not occur; correction factor to account for inverse dose-rate effect under conditions of chronic exposure to alpha particles is applied in all cases.

[d]Distribution is the same as that assumed for leukemias induced by acute exposure to 0.1-2 MeV neutrons (see Table IV.H.3).

Table IV.H.3. Neutrons: Summary of probability distributions of radiation effectiveness factors to be used in estimating cancer risks and assigned shares in accordance with eq. (IV.H.2) or (IV.H.3)[a]

Cancer type	Exposure	Probability distribution of radiation effectiveness factor (REF_L)
Leukemia[b]	Chronic or acute[c]	
Neutron energies		
E = 0.1-2 MeV[d]		Lognormal distribution with 95% confidence interval between 2.0 and 60
E = 10-100 keV; E = 2-20 MeV		Stepwise uniform distribution with – 30% probability assigned to values from 1.0 to 4.0; 50% probability assigned to values from 4.0 to 8.0; 20% probability assigned to values from 8.0 to 40
E < 10 keV; E > 20 MeV		Stepwise uniform distribution with – 30% probability assigned to values from 1.0 to 2.3; 50% probability assigned to values from 2.3 to 3.5; 20% probability assigned to values from 3.5 to 25

Table is continued on following page.

Table IV.H.3. Neutrons: Summary of probability distributions of radiation effectiveness factors (continued)

Cancer type	Exposure	Probability distribution of radiation effectiveness factor (REF_H)
Solid tumors	Chronic or acute[c]	
Neutron energies		
E = 0.1-2 MeV[d]		Lognormal distribution with 95% confidence interval between 2.0 and 30
E = 10-100 keV; E = 2-20 MeV		Stepwise uniform distribution with – 30% probability assigned to values from 1.0 to 3.0; 50% probability assigned to values from 3.0 to 5.0; 20% probability assigned to values from 5.0 to 20
E < 10 keV; E > 20 MeV		Stepwise uniform distribution with – 30% probability assigned to values from 1.0 to 1.6; 50% probability assigned to values from 1.6 to 2.4; 20% probability assigned to values from 2.4 to 12
Correction for inverse dose-rate effect for chronic exposures to neutrons – Discrete distribution with – 50% probability assigned to value 1.0; 30% probability assigned to value 1.5; 15% probability assigned to value 2.0; 5% probability assigned to value 3.0		

[a]The equations are given in Section IV.H of the report. Equation (IV.H.2) applies to solid tumors, and eq. (IV.H.3) applies to leukemias.

[b]Assumed probability distributions apply to leukemias, lymphomas, and lymphocytic cancers.

[c]Under conditions of chronic exposure only, correction factor to account for inverse dose-rate effect is applied.

[d]Energy range includes spectrum of fission neutrons.

Table IV.I.1. Factors for adjusting the lung cancer ERR_{1Sv} for smoking status under the assumption of an additive interaction model.

	Used in the 1985 report		Used in deriving uncertainty distribution for this report (W_S*)	
Smoking category (S)	Males	Females	Males	Females
Total	1.00	1.00	1.00	1.00
Never smokers	6.81	4.64	4.74	3.90
Former smokers	1.71	1.17	1.19	0.98
Present smokers (all)	0.604	0.411	0.42	0.35
<10 cigarettes/day	1.75	1.19	1.22	1.00
10-20 cigarettes/day	0.71	0.48	0.49	0.41
21-39 cigarettes/day	0.41	0.28	0.28	0.23
40+ cigarettes/day	0.29	0.20	0.20	0.16
Ever smoker (Present and former smokers)	0.73	0.47	0.51	0.41

Table IV.I.2. Percentage of the U.S. population in various smoking categories

	Used in the 1985 report (Status in 1964-65)		Used in this report (Status in 1993)	
Smoking category (S)	Males	Females	Males	Females
Never smokers	29.8	59.0	42.4	57.8
Former smokers	19.2	7.8	29.9	19.7
Current smokers (all)	51.0	33.2	27.7	22.5
<10 cigarettes/day	13.6	13.5	7.4*	9.2*
10-20 cigarettes/day	24.7	15.0	13.4*	10.2*
21-39 cigarettes/day	11.2	4.4	6.1*	3.0*
40+ cigarettes/day	1.4	0.3	0.8*	0.2*

*These percentages were obtained by assuming distribution by amount smoked among current smokers was the same as that used in the 1985 report (p.50)

Appendix Table C.1. Comparison of approach 1 and approach 2 for estimating the 99% upper statistical uncertainty limit for assigned share, by ages at exposure and at diagnosis. Tabulated values are the approach 2 estimate, in percent, for a 50% approach 1 estimate.

Sex, cancer site		Age at	Age at cancer diagnosis					
corr(log α, γ)	*corr(log α, δ)*	exposure	25	30	35	40	45	≥50
Male, all digestive cancers		18	50.9	51.5	52.2	52.8	53.3	53.5
		20		51.0	51.7	52.3	52.7	53.0
.314	*-.082*	25			50.3	50.8	51.2	51.6
		≥30				49.3	49.7	50.0
Female, all digestive cancers		18	51.8	52.4	53.0	53.5	53.6	53.3
		20		51.9	52.5	53.0	53.2	53.0
.343	*-.011*	25			51.1	51.5	51.7	51.7
		≥30				49.9	50.0	50.0
Female, stomach cancer		18	52.4	52.8	53.2	53.3	53.2	52.9
		20		52.4	52.7	52.9	52.8	52.5
.279	*.031*	25			51.5	51.6	51.6	51.4
		≥30				50.2	50.1	50.0
Both sexes, liver cancer		18	50.2	51.0	51.8	52.5	53.1	53.5
		20		50.5	51.2	51.9	52.5	53.0
.307	*-.115*	25			49.8	50.4	51.0	51.6
		≥30				49.0	49.5	50.0
Female, breast cancer		18	52.1	53.2	54.6	56.0	56.6	56.5
		20		52.4	53.6	54.9	55.8	55.8
.589	*-.107*	25			51.1	51.9	52.7	53.2
		≥30				49.2	49.6	50.0

Appendix Table E.1. Comparison of ERR values as calculated using CIRRPC and IREP. Tabulated ERR values are for a male (female in the case of breast cancer) who developed cancer at age 55 (unless indicated otherwise) following exposure to a chronic dose of 1cSv at age 20.

(1) Type of Cancer	(2) ERR85[1] at 1 cSv, ×100	(3) Dose and linearity factor[2], FDL	(4) **FDL ×ERR85 at 1 cSv, ×100**	(5) Baseline factor[3] PB	(6) FDL × PB× ERR85 at 1 cSv, ×100	(7) **IREP ERR at 1 cSv, ×100**
Leukemia except CLL						
Peak[6]	6.13	2.43	**14.9**	1.2	17.9	**16.8**
15 years afer exposure	2.05	2.43	**5.0**	1.2	6.0	**4.6**
30 years after exposure	0.23	2.43	**0.56**	1.2	0.68	**0.67**
Acute Myeloid Leuk.						
Peak[6]	5.96	2.43	**14.5**	1.2	17.4	**5.1**
15 years after exposure	1.87	2.43	**4.6**	1.2	5.5	**2.9**
30 years after exposure	0.15	2.43	**0.35**	1.2	0.42	**1.2**
Chronic Myeloid Leuk.						
Peak[6]	6.35	2.43	**15.4**	1.2	18.5	**26.9**
15 years after exposure	2.51	2.43	**6.1**	1.2	7.3	**2.3**
30 years after exposure	0.62	2.43	**1.5**	1.2	1.8	**0.06**
Esophagus	0.207	2.43	**0.50**	2.3	1.16	**0.34**
Stomach	0.569	2.43	**1.5**	1.9	2.6	**0.22**
Colon	0.167	2.43	**0.41**	2.4	0.97	**0.47**
Liver	2.81	2.43	**6.9**	2.6	17.9	**1.28**
Pancreas	0.446	2.43	**1.1**	1.9	2.1	**0.10**
Lung (Non-smoker)	0.831	2.43	**2.0**	2.2	4.44	**0.38**
Lung (Smoker)	0.074	2.43	**0.18**	2.2	0.40	**0.16**
Urinary	0.124	2.43	**0.30**	4.1	1.24	**0.46 or 0.35[5]**
Female Breast	0.606	1.00	**0.61**	1.9	1.15	**0.38**
Thyroid	2.82	1.00	**2.8**	2.7	6.3	**1.2**

[1]The ERR at 1 cSv as given by NIH (1985)

[2]For non-linear estimates based on the A-bomb survivor data, the factor includes 1.62 to correct for dosimetry-related bias and 1.5 to correct for a one-third probability of a linear dose-response.

[3]To calculate CIRRPC screening doses, ERRs were adjusted upward to consider the possibility that a subject might have an exceptionally low baseline risk. These factors were obtained as ratio of average U.S. rate divided by the 10th percentile of the distribution for all U.S. counties.

[4]These are ERRs based on 5000 iterations with IREP.

[5]The first value is that for all urinary cancers; the second is that for bladder cancer.

[6]This the maximum ERR for all time periods after exposure. For the NIH tables, this occurred in the period 3-8 years following exposure. For IREP, the maximum occurred five years after exposure.

Appendix Table E.2. Comparison of ERR values as calculated using CIRRPC and IREP. Tabulated ERR values are for a male (female in the case of breast cancer) who developed cancer at age 55 (unless indicated otherwise) following exposure to a chronic dose of 1cSv at age 30.

(1) Type of Cancer	(2) ERR85[1] at 1 cSv, ×100	(3) Dose and linearity factor[2], FDL	(4) **FDL ×ERR85 at 1 cSv, ×100**	(5) Baseline Factor[3], FB	(6) FDL × FB× ERR85 at 1 cSv, ×100	(7) **IREP ERR at 1 cSv, ×100**
Leukemia except CLL						
Peak[6]	3.95	2.43	**9.6**	1.2	11.5	**10.4**
15 years afer exposure	1.73	2.43	**4.2**	1.2	5.0	**3.7**
30 years after exposure	0.17	2.43	**0.41**	1.2	0.50	**0.75**
Acute Myeloid Leuk.						
Peak[6]	3.75	2.43	**9.0**	1.2	10.8	**5.1**
15 years after exposure	1.63	2.43	**3.9**	1.2	4.7	**2.9**
30 years after exposure	0.15	2.43	**0.36**	1.2	0.44	**1.2**
Chronic Myeloid Leuk.						
Peak[6]	5.49	2.43	**13.3**	1.2	16.0	**26.9**
15 years after exposure	2.15	2.43	**5.2**	1.2	6.3	**2.3**
30 years after exposure	0.27	2.43	**0.66**	1.2	0.79	**0.06**
Esophagus	0.077	2.43	**0.19**	2.3	0.43	**0.21**
Stomach	0.270	2.43	**0.66**	1.9	1.25	**0.13**
Colon	0.077	2.43	**0.19**	2.4	0.45	**0.28**
Liver	0.843	2.43	**2.05**	2.6	5.3	**0.76**
Pancreas	0.176	2.43	**0.43**	1.9	0.81	**0.06**
Lung (Non-smoker)	0.366	2.43	**0.89**	2.2	2.0	**0.38**
Lung (Smoker)	0.032	2.43	**0.08**	2.2	0.17	**0.16**
Urinary	0.064	2.43	**0.16**	4.1	0.64	**0.27 or 0.20[5]**
Female Breast	0.268	1.00	**0.27**	1.9	0.51	**0.26**
Thyroid	1.19	1.00	**1.19**	2.7	3.2	**0.53**

Footnotes are the same as in Appendix Table E.1

Appendix Table E.3. Comparison of ERR values as calculated using CIRRPC and IREP. Tabulated ERR values are for a male (female in the case of breast cancer) who developed cancer at age 55 (unless indicated otherwise) following exposure to a chronic dose of 1cSv at age 40.

(1) Type of Cancer	(2) ERR85[1] at 1 cSv, ×100	(3) Dose and linearity factor[2], FDL	(4) **FDL ×ERR85 at 1 cSv, ×100**	(5) Baseline Factor[3], FB	(6) FDL × FB× ERR85 at 1 cSv, ×100	(7) **IREP ERR at 1 cSv, ×100**
Leukemia except CLL						
Peak[6]	2.04	2.43	**4.9**	1.2	5.8	**6.5**
15 years afer exposure	1.21	2.43	**2.9**	1.2	3.5	**2.9**
30 years after exposure	0.16	2.43	**0.39**	1.2	0.47	**0.85**
Acute Myeloid Leuk.						
Peak[6]	1.63	2.43	**4.0**	1.2	4.8	**5.1**
15 years after exposure	1.21	2.43	**2.9**	1.2	3.5	**2.9**
30 years after exposure	0.16	2.43	**0.39**	1.2	0.47	**1.2**
Chronic Myeloid Leuk.						
Peak[6]	4.93	2.43	**12.0**	1.2	14.4	**26.9**
15 years after exposure	1.10	2.43	**2.7**	1.2	3.2	**2.3**
30 years after exposure	0.18	2.43	**0.44**	1.2	0.52	**0.06**
Esophagus	0.044	2.43	**0.11**	2.3	0.25	**0.21**
Stomach	0.150	2.43	**0.36**	1.9	0.69	**0.13**
Colon	0.038	2.43	**0.09**	2.4	0.22	**0.28**
Liver	0.331	2.43	**0.80**	2.6	2.1	**0.76**
Pancreas	0.094	2.43	**0.23**	1.9	0.43	**0.06**
Lung (Non-smoker)	0.221	2.43	**0.54**	2.2	1.2	**0.38**
Lung (Smoker)	0.032	2.43	**0.08**	2.2	0.17	**0.16**
Urinary	0.040	2.43	**0.10**	4.1	0.40	**0.27 or 0.20[5]**
Female Breast	0.100	1.00	**0.10**	1.9	0.19	**0.26**
Thyroid	1.11	1.00	**1.11**	2.7	3.0	**0.23**

Footnotes are the same as in Appendix Table E.1

Appendix Table E.4. Comparison of 99% screening doses (in cSv) from CIRRPC and IREP for males (except breast cancer) exposed to a chronic dose at age 20, 30, or 40 and who developed cancer at age 55 (unless indicated otherwise)

Type of Cancer	99% screening doses for exposure at age 20		99% screening doses for exposure at age 30		99% screening doses for exposure at age 40	
	CIRRPC[1]	IREP[2]	CIRRPC[1]	IREP[2]	CIRRPC[1]	IREP[2]
Leukemia except CLL						
Peak[3]	1.1 (1.3)	2.2	1.7 (2.0)	4.2	3.3 (4.0)	6.5
15 years after exposure[4]	3.3 (3.9)	11	3.9 (4.6)	15	5.5 (6.6)	19
Acute Myeloid Leuk.						
Peak[3]	1.1 (1.3)	5.8	[illegible]	5.8	4.1 (4.9)	5.8
15 years after exposure[4]	3.5 (4.2)	16	[illegible] (4.9)	16	5.5 (6.6)	16
Chronic Myeloid Leuk.						
Peak[3]	0.9 (1.1)	1.2	1.3 (1.6)	1.2	1.4 (1.7)	1.2
15 years after exposure[4]	2.7 (3.2)	11	3.2 (3.8)	11	5.9 (7.1)	11
Esophagus	3.9 (8.6)	45	9.9 (21)	80	17 (34)	80
Stomach	6.9 (12)	34	14 (24)	64	23 (41)	64
Colon	17 (36)	49	33 (65)	90	58 (108)	90
Liver	1.0 (2.6)	14	3.3 (8.2)	23	8.2 (20)	23
Pancreas	5.8 (11)	122	14 (24)	226	24 (41)	226
Lung (Non-smoker)[5]	4.3 (9.1)	51	9.3 (19)	51	15 (30)	51
Urinary	13 (44)	55 or 62[6]	23 (71)	99 or 111[6]	35 (100)	99 or 111[6]
Female Breast	22[7] (41)	63	49[7] (93)	80	132[7] (251)	80
Thyroid	3.4[7] (9.2)	8.5	7.9[7] (21)	21	9.5[7] (26)	34

[1]The main entries are the screening doses (in cSv) as given by CIRRPC, Table 3. The entries in parentheses are the screening doses that would have been obtained without the assumption that subjects had exceptionally low baseline risks.

[2]These screening doses were based on 5000 iterations with IREP. No uncertainty was included for the dose estimate.

[3]CIRRPC screening doses for leukemia within 20 years of exposure were based on the time since exposure that resulted in the maximum ERR. For IREP, the maximum occurred five years after exposure.

[4]CIRRPC screening doses for leukemia 20 or more years after exposure were based on ERRs 15 years after exposure.

[5]CIRRPC screening doses for lung cancer in persons for whom smoking status was unknown at the time of screening were based on non-smokers. CIRRPC screening doses for lung cancer for persons known to be smokers at the time of screening were based on the assumption that smoking status was unknown, a category that was not available in IREP.

[6]The first screening dose is based on all urinary cancers (used in IREP for urinary cancer other than bladder), and the second screening dose is based on bladder cancer.

[7]The CIRRPC screening doses for female breast and thyroid cancer were incorrectly based on a linear-quadratic dose-response function. The values above correct this error and are based on a linear dose-response function.